



## UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No. 1606.0020001	
First Inventor or Application Identifier Peter G. BROWN	
Title	System and Method for Simulation, Modeling and Scheduling of Solution Preparation in Biopharmaceutical Batch Process Manufacturing Facilities
Express Mail Label No.	

## APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231

1. ☒ \* Fee Transmittal Form (e.g., PTO/SB/17)  
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 99]  
(Preferred arrangement set forth below)  
- Descriptive title of the invention  
- Cross References to Related Applications  
- Background of the Invention  
- Brief Summary of the Invention  
- Brief Description of the Drawings (if filed)  
- Detailed Description  
- Claims  
- Abstract of the Disclosure
3. ☒ Drawings (35 U.S.C. 113) [Total Sheets 105]
4. ☒ Oath or Declaration [Total Pages 2]  
a. ☒ Newly executed (original)  
b. ☐ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]
1. ☐ DELETION OF INVENTOR(S)  
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR §§ 1.63(d)(2) and 1.33(b)
5. ☐ Incorporation By Reference (useable if Box 4b is checked)  
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)  
a. ☐ Computer Readable Copy  
b. ☐ Paper Copy (identical to computer copy)  
c. ☐ Statement verifying identity of above copies

## ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcards (MPEP 503) (Should be specifically itemized)
14. ☐ \*Small Entity Statement(s) (PTO/SB/09-12) ☒ Statement filed in prior application, Status still proper and desired
15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. ☒ Other: 37 C.F.R. § 1.136(a)(3) Authorization ☐ Other
- \*NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28)

17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment

☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No.      /     

Prior application information: Examiner                      Group/Art Unit:                     

## 18. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label

(Insert Customer No. or Attach bar code label here)

or ☒ Correspondence address below

NAME	STERN, KESSLER, GOLDSTEIN & FOX P.L.L.C.			
	Attorneys at Law			
ADDRESS	Suite 600, 1100 New York Avenue, NW			
CITY	Washington	STATE	DC	ZIP CODE 20005-3934
COUNTRY	USA	TELEPHONE	(202) 371-2600	FAX (202) 371-2540

NAME (Print/Type)	Robert Joseph	Registration No. (Attorney/Agent)	36,013
SIGNATURE		Date	6/19/98

<b>FEE TRANSMITTAL</b>		<b>Complete if Known</b>	
<i>Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 1997. Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB-09-12. See 37 C.F.R. §§ 1.27 and 1.28.</i>		Application Number	To be assigned
		Filing Date	June 19, 1998
		First Named Inventor	Peter G. BROWN
		Examiner Name	To be assigned
		Group / Art Unit	To be assigned
TOTAL AMOUNT OF PAYMENT		Attorney Docket Number	1606.0020001/RES/RVM
(\$)			

METHOD OF PAYMENT (check one)	FEE CALCULATION (continued)																																																																																																																																																																						
<p>1. <input type="checkbox"/> The Commissioner is hereby authorized to charge indicated fees and credit any overpayment to</p> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <tr> <td style="width: 30%;">Deposit Account Number</td> <td style="width: 70%;">19-0036</td> </tr> <tr> <td>Deposit Account Name</td> <td>Sterne, Kessler, Goldstein &amp; Fox P.L.L.C.</td> </tr> </table> <p><input type="checkbox"/> Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17      <input type="checkbox"/> Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance</p> <p>2. <input checked="" type="checkbox"/> Payment Enclosed.      <input checked="" type="checkbox"/> Check No. _____</p> <p><input type="checkbox"/> Money Order      <input checked="" type="checkbox"/> Other*</p> <p>*Charge any deficiencies or credit any overpayments in the fees or fee calculations of Parts 1, 2 and 3 below to Deposit Account No. 19-0036</p>	Deposit Account Number	19-0036	Deposit Account Name	Sterne, Kessler, Goldstein & Fox P.L.L.C.	<p>3. ADDITIONAL FEES</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>105</td><td>130</td><td>205</td><td>65</td><td>Surcharge - late filing fee or oath</td><td></td></tr> <tr><td>127</td><td>50</td><td>227</td><td>25</td><td>Surcharge - late provisional filing fee or cover sheet</td><td></td></tr> <tr><td>139</td><td>130</td><td>139</td><td>130</td><td>Non-English specification</td><td></td></tr> <tr><td>147</td><td>2,520</td><td>147</td><td>2,520</td><td>For filing a request for reexamination</td><td></td></tr> <tr><td>112</td><td>920*</td><td>112</td><td>920*</td><td>Requesting publication of SIR prior to Examiner action</td><td></td></tr> <tr><td>113</td><td>1,840*</td><td>113</td><td>1,840*</td><td>Requesting publication of SIR after Examiner action</td><td></td></tr> <tr><td>115</td><td>110</td><td>215</td><td>55</td><td>Extension for reply within first month</td><td></td></tr> <tr><td>116</td><td>400</td><td>216</td><td>200</td><td>Extension for reply within second month</td><td></td></tr> <tr><td>117</td><td>950</td><td>217</td><td>475</td><td>Extension for reply within third month</td><td></td></tr> <tr><td>118</td><td>1,510</td><td>218</td><td>755</td><td>Extension for reply within fourth month</td><td></td></tr> <tr><td>128</td><td>2,060</td><td>228</td><td>1,030</td><td>Extension for reply within fifth month</td><td></td></tr> <tr><td>119</td><td>310</td><td>219</td><td>155</td><td>Notice of Appeal</td><td></td></tr> <tr><td>120</td><td>310</td><td>220</td><td>155</td><td>Filing a brief in support of an appeal</td><td></td></tr> <tr><td>121</td><td>270</td><td>221</td><td>135</td><td>Request for oral hearing</td><td></td></tr> <tr><td>138</td><td>1,510</td><td>138</td><td>1,510</td><td>Petition to institute a public use proceeding</td><td></td></tr> <tr><td>140</td><td>110</td><td>240</td><td>55</td><td>Petition to revive - unavoidable</td><td></td></tr> <tr><td>141</td><td>1,320</td><td>241</td><td>660</td><td>Petition to revive - unintentional</td><td></td></tr> <tr><td>142</td><td>1,320</td><td>242</td><td>660</td><td>Utility issue fee (or reissue)</td><td></td></tr> <tr><td>143</td><td>450</td><td>243</td><td>225</td><td>Design issue fee</td><td></td></tr> <tr><td>144</td><td>670</td><td>244</td><td>335</td><td>Plant issue fee</td><td></td></tr> <tr><td>122</td><td>130</td><td>122</td><td>130</td><td>Petitions to the Commissioner</td><td></td></tr> <tr><td>123</td><td>50</td><td>123</td><td>50</td><td>Petitions related to provisional applications</td><td></td></tr> <tr><td>126</td><td>240</td><td>126</td><td>240</td><td>Submission of Information Disclosure Stmt</td><td></td></tr> <tr><td>581</td><td>40</td><td>581</td><td>40</td><td>Recording each patent assignment per property (times number of properties)</td><td></td></tr> <tr><td>146</td><td>790</td><td>246</td><td>395</td><td>Filing a submission after final rejection (37 CFR 1.129(a))</td><td></td></tr> <tr><td>149</td><td>790</td><td>249</td><td>395</td><td>For each additional invention to be examined (37 CFR 1.129(b))</td><td></td></tr> </tbody> </table> <p>Other fee (specify) _____ Other fee (specify) _____ *Reduced by Basic Filing Fee Paid</p>	Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	105	130	205	65	Surcharge - late filing fee or oath		127	50	227	25	Surcharge - late provisional filing fee or cover sheet		139	130	139	130	Non-English specification		147	2,520	147	2,520	For filing a request for reexamination		112	920*	112	920*	Requesting publication of SIR prior to Examiner action		113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action		115	110	215	55	Extension for reply within first month		116	400	216	200	Extension for reply within second month		117	950	217	475	Extension for reply within third month		118	1,510	218	755	Extension for reply within fourth month		128	2,060	228	1,030	Extension for reply within fifth month		119	310	219	155	Notice of Appeal		120	310	220	155	Filing a brief in support of an appeal		121	270	221	135	Request for oral hearing		138	1,510	138	1,510	Petition to institute a public use proceeding		140	110	240	55	Petition to revive - unavoidable		141	1,320	241	660	Petition to revive - unintentional		142	1,320	242	660	Utility issue fee (or reissue)		143	450	243	225	Design issue fee		144	670	244	335	Plant issue fee		122	130	122	130	Petitions to the Commissioner		123	50	123	50	Petitions related to provisional applications		126	240	126	240	Submission of Information Disclosure Stmt		581	40	581	40	Recording each patent assignment per property (times number of properties)		146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))		149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	
Deposit Account Number	19-0036																																																																																																																																																																						
Deposit Account Name	Sterne, Kessler, Goldstein & Fox P.L.L.C.																																																																																																																																																																						
Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid																																																																																																																																																																		
105	130	205	65	Surcharge - late filing fee or oath																																																																																																																																																																			
127	50	227	25	Surcharge - late provisional filing fee or cover sheet																																																																																																																																																																			
139	130	139	130	Non-English specification																																																																																																																																																																			
147	2,520	147	2,520	For filing a request for reexamination																																																																																																																																																																			
112	920*	112	920*	Requesting publication of SIR prior to Examiner action																																																																																																																																																																			
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action																																																																																																																																																																			
115	110	215	55	Extension for reply within first month																																																																																																																																																																			
116	400	216	200	Extension for reply within second month																																																																																																																																																																			
117	950	217	475	Extension for reply within third month																																																																																																																																																																			
118	1,510	218	755	Extension for reply within fourth month																																																																																																																																																																			
128	2,060	228	1,030	Extension for reply within fifth month																																																																																																																																																																			
119	310	219	155	Notice of Appeal																																																																																																																																																																			
120	310	220	155	Filing a brief in support of an appeal																																																																																																																																																																			
121	270	221	135	Request for oral hearing																																																																																																																																																																			
138	1,510	138	1,510	Petition to institute a public use proceeding																																																																																																																																																																			
140	110	240	55	Petition to revive - unavoidable																																																																																																																																																																			
141	1,320	241	660	Petition to revive - unintentional																																																																																																																																																																			
142	1,320	242	660	Utility issue fee (or reissue)																																																																																																																																																																			
143	450	243	225	Design issue fee																																																																																																																																																																			
144	670	244	335	Plant issue fee																																																																																																																																																																			
122	130	122	130	Petitions to the Commissioner																																																																																																																																																																			
123	50	123	50	Petitions related to provisional applications																																																																																																																																																																			
126	240	126	240	Submission of Information Disclosure Stmt																																																																																																																																																																			
581	40	581	40	Recording each patent assignment per property (times number of properties)																																																																																																																																																																			
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))																																																																																																																																																																			
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))																																																																																																																																																																			
<p style="text-align: center;"><b>FEE CALCULATION</b></p> <p>1. BASIC FILING FEE</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>101</td><td>790</td><td>201</td><td>395</td><td>Utility filing fee</td><td>395.00</td></tr> <tr><td>106</td><td>330</td><td>206</td><td>165</td><td>Design filing fee</td><td></td></tr> <tr><td>107</td><td>540</td><td>207</td><td>270</td><td>Plant filing fee</td><td></td></tr> <tr><td>108</td><td>790</td><td>208</td><td>395</td><td>Reissue filing fee</td><td></td></tr> <tr><td>114</td><td>150</td><td>214</td><td>75</td><td>Provisional filing fee</td><td></td></tr> </tbody> </table> <p style="text-align: right;">SUBTOTAL (1) (\$)</p> <p>2. EXTRA CLAIM FEES</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr> <td>Total Claims</td> <td>3</td> <td>- 20** =</td> <td>0</td> <td>X</td> <td>= 0</td> </tr> <tr> <td>Indep. Claims</td> <td>1</td> <td>- 3** =</td> <td>0</td> <td>X</td> <td>= 0</td> </tr> <tr> <td colspan="6">Multiple Dependent Claims _____ = 0</td> </tr> </tbody> </table> <p>** or number previously paid, if greater; For Reissues see below</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Large Fee Code</th> <th>Entity Fee (\$)</th> <th>Small Fee Code</th> <th>Entity Fee (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>103</td><td>22</td><td>203</td><td>11</td><td>Claims in excess of 20</td><td></td></tr> <tr><td>102</td><td>82</td><td>202</td><td>41</td><td>Independent claims in excess of 3</td><td></td></tr> <tr><td>104</td><td>270</td><td>204</td><td>135</td><td>Multiple dependant claim</td><td></td></tr> <tr><td>108</td><td>82</td><td>208</td><td>41</td><td>**Reissue independent claims over original patent</td><td></td></tr> <tr><td>110</td><td>22</td><td>210</td><td>11</td><td>**Reissue claims in excess of 20 and over original patent</td><td></td></tr> </tbody> </table> <p style="text-align: right;">SUBTOTAL (2) (\$)</p>	Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	101	790	201	395	Utility filing fee	395.00	106	330	206	165	Design filing fee		107	540	207	270	Plant filing fee		108	790	208	395	Reissue filing fee		114	150	214	75	Provisional filing fee		Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	Total Claims	3	- 20** =	0	X	= 0	Indep. Claims	1	- 3** =	0	X	= 0	Multiple Dependent Claims _____ = 0						Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid	103	22	203	11	Claims in excess of 20		102	82	202	41	Independent claims in excess of 3		104	270	204	135	Multiple dependant claim		108	82	208	41	**Reissue independent claims over original patent		110	22	210	11	**Reissue claims in excess of 20 and over original patent		<p style="text-align: center;">SUBTOTAL (3) (\$)</p>																																																																						
Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid																																																																																																																																																																		
101	790	201	395	Utility filing fee	395.00																																																																																																																																																																		
106	330	206	165	Design filing fee																																																																																																																																																																			
107	540	207	270	Plant filing fee																																																																																																																																																																			
108	790	208	395	Reissue filing fee																																																																																																																																																																			
114	150	214	75	Provisional filing fee																																																																																																																																																																			
Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid																																																																																																																																																																		
Total Claims	3	- 20** =	0	X	= 0																																																																																																																																																																		
Indep. Claims	1	- 3** =	0	X	= 0																																																																																																																																																																		
Multiple Dependent Claims _____ = 0																																																																																																																																																																							
Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid																																																																																																																																																																		
103	22	203	11	Claims in excess of 20																																																																																																																																																																			
102	82	202	41	Independent claims in excess of 3																																																																																																																																																																			
104	270	204	135	Multiple dependant claim																																																																																																																																																																			
108	82	208	41	**Reissue independent claims over original patent																																																																																																																																																																			
110	22	210	11	**Reissue claims in excess of 20 and over original patent																																																																																																																																																																			

SUBMITTED BY		Complete (if applicable)	
Typed or Printed Name	Robert Sokohl	Reg. Number	36,013
Signature		Date	6/19/98
		Deposit Acct. User ID	

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

ATTORNEYS AT LAW

SUITE 600

1100 NEW YORK AVENUE, N.W.

WASHINGTON, D.C. 20005-3934

(202) 371-2600

FACSIMILE (202) 371-2540, (202) 371-6566

ROBERT GREENE STERNE  
EDWARD J. KESSLER  
SERGE A. GOLDSTEIN  
SAMUEL L. FOX  
DAVID K.S. CORNWELL  
ROBERT W. ESMOND  
TRACY-GENE G. DURKIN  
MICHELE A. CIMBALA  
MICHAEL B. RAY  
ROBERT E. SOKOHL  
ERIC K. STEFFE  
MICHAEL Q. LEE

JOHN M. COVERT\*  
LINDA E. ALCORN  
RAZ E. FLESHNER  
ROBERT C. MILLONIG  
STEVEN R. LUDWIG  
MICHAEL V. MESSINGER  
JUDITH U. KIM\*  
KEITH KIND  
TIMOTHY J. SHEA, JR.  
DONALD R. MCPHAIL  
PATRICK E. GARRETT  
BARBARA A. PARVIS  
MICHAEL A. RAHMAN\*

STEPHEN G. WHITESIDE\*  
NOEL B. WHITLEY\*  
JEFFREY T. HELVEY\*  
RICHARD A. DUNNING, JR.  
KIMBERLIN M. TOOHEY  
RALPH P. ALBRECHT  
HEIDI L. KRAUS\*  
JEFFREY R. KURIN\*  
CARL B. MASSEY, JR.\*  
RAYMOND MILLIEN\*  
PATRICK D. O'BRIEN\*  
BRIAN S. ROSENBLUM\*

DONALD J. FEATHERSTONE\*\*  
LAWRENCE B. BUGAISKY\*\*  
KAREN R. MARKOWICZ\*\*  
GRANT E. REED\*\*  
VICTOR E. JOHNSON\*\*  
SERGE SIRA\*\*

\*BAR OTHER THAN D.C.  
\*\*REGISTERED PATENT AGENTS

WRITER'S DIRECT NUMBER

June 19, 1998

INTERNET ADDRESS

Assistant Commissioner for Patents  
Washington, D.C. 20231

**Box Patent Application**

Re: U.S. Non-Provisional Utility Patent Application under 37 C.F.R. § 1.53(b)  
Appl. No. To be assigned; Filed: June 19, 1998  
(From Provisional Appl. No. 60/050,294, Filed: June 20, 1997)  
For: **System and Method for Simulation, Modeling and Scheduling of  
Solution Preparation in Biopharmaceutical Batch Process  
Manufacturing Facilities**

Inventor: Peter G. BROWN  
Our Ref: 1606 0020001

Sir,

The following documents are forwarded herewith for appropriate action by the U.S.  
Patent and Trademark Office:

1. PTO Utility Patent Application Transmittal Form (PTO/SB/05),
2. U.S. Utility Patent Application entitled:

**System and Method for Simulation, Modeling and Scheduling of Solution  
Preparation in Biopharmaceutical Batch Process Manufacturing Facilities**

and naming as inventor

**Peter G. Brown**

Assistant Commissioner for Patents

June 19, 1998

Page 2

the application comprising:

a. A specification containing:

(i) 90 pages of description prior to the claims;

(ii) 1 page of claims (3 claims),

(iii) a one (1) page abstract;

(iv) 7 pages of Appendices A1-A7;

b. One-Hundred and Five (105) sheets of drawings (Figures 1-11, 12A-H, 13-35, 36A-H, 37A-B, 38-41, 42A-D, 43-44, 45A-I, 46-63, 64A-Z, 64AA-64AB),

c. An original executed combined Declaration and Power of Attorney for Patent Application;

3 PTO Fee Transmittal Form PTO/SB/17 (in duplicate);

4. Authorization to Treat a Reply As Incorporating An Extension of Time Under 37 C.F.R. § 1.136(a)(3) (in duplicate),

5 Our check No. 22125 for \$395.00 to cover:

\$395.00 Filing fee for patent application; and

6 Two (2) return postcards.

It is respectfully requested that, of the two attached postcards, one be stamped with the filing date of these documents and returned to our courier, and the other, prepaid postcard, be stamped with the filing date and unofficial application number and returned as soon as possible.

Assistant Commissioner for Patents

June 19, 1998

Page 3

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed

***This patent application claims priority, under 35 U.S.C. § 119(e), to U.S. Provisional Application No. 60/050,294, filed June 20, 1997.***

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert Sokohl  
Attorney for Applicant  
Registration No. 36,013

[illegible]

2

## 10

15

20

25

● "System and Method for Simulation, Modeling and Scheduling of Equipment Maintenance and Calibration in Biopharmaceutical Batch Process Manufacturing Facilities", by Brown, having application number TBA (Attorney Docket No. 1606.0040001), filed concurrently herewith; and

- "System and Method for Simulation, Modeling and Scheduling of Quality Control Sampling in Biopharmaceutical Batch Process Manufacturing Facilities", by Brown, having application number TBA (Attorney Docket No. 1606 0050001), filed concurrently herewith.

SKGF Ref. No. 1606.0020001

## ***Background of the Invention***

### ***Field of the Invention***

The present invention relates generally to the design of large scale batch manufacturing facilities, and specifically to the design of biopharmaceutical drug manufacturing processes.

### ***Related Art***

Biopharmaceutical plants produce biopharmaceutical products through biological methods. Typical biopharmaceutical synthesis methods are mammalian cell culture, microbial fermentation and insect cell culture. Occasionally biopharmaceutical products are produced from natural animal or plant sources or by a synthetic technique called solid phase synthesis. Mammalian cell culture, microbial fermentation and insect cell culture involve the growth of living cells and the extraction of biopharmaceutical products from the cells or the medium surrounding the cells. Solid phase synthesis and crude tissue extraction are processes by which biopharmaceuticals are synthesized from chemicals or extracted from natural plant or animal tissues, respectively.

The process for producing biopharmaceuticals is complex. In addition to basic synthesis, additional processing steps of separation, purification, conditioning and formulation are required to produce the end product biopharmaceutical. Each of these processing steps includes additional unit operations. For example, the step of purification may include the step of Product Adsorption Chromatography, which may further include the unit operations of High Pressure Liquid Chromatography (HPLC), Medium Pressure Liquid Chromatography (MPLC), Low Pressure Liquid Chromatography (LPLC), etc. The production of biopharmaceuticals is complex because of the number,

complexity and combinations of synthesis methods and processing steps possible. Consequently, the design of a biopharmaceutical plant is expensive.

Tens of millions of dollars can be misspent during the design and construction phases of biopharmaceutical plants due to inadequacies in the design process. Errors and inefficiencies are introduced in the initial design of the biopharmaceutical production process because no effective tools for modeling and simulating a biopharmaceutical production process exists. The inadequacies in the initial process design carry through to all phases of the biopharmaceutical plant design and construction. Errors in the basic production process design propagate through all of the design and construction phases, resulting in increased cost due to change orders late in the facility development project. For example, detailed piping and instrumentation diagrams (P&IS) normally cost thousands of dollars per diagram. Problems in the biopharmaceutical production process design frequently necessitate the re-working of these detailed P&IS. This adds substantially to the overall cost of design and construction of a biopharmaceutical plant

There are generally three phases of biopharmaceutical plants which coincide with the different levels of drug approval by the FDA. A Clinical Phase I/II biopharmaceutical plant produces enough biopharmaceutical product to support both phase I and phase II clinical testing of the product which may involve up to a few hundred patients. A Clinical Phase III biopharmaceutical plant produces enough biopharmaceutical product to support two to three-thousand patients during phase III clinical testing. A Clinical Phase III plant will also produce enough of the biopharmaceutical drug to support an initial commercial offering upon the licensing of the drug by the FDA for commercial sale. The successive phases represent successively larger biopharmaceutical facilities to support full scale commercial production after product licensing. Often the production process design is repeated for each phase, resulting in increased costs to each phase of plant development.



The design, architecture and engineering of biopharmaceutical plants is a several hundred million dollars a year industry because of the complex nature of biopharmaceutical production. Design of biopharmaceutical plants occurs in discrete phases. The first phase is the conceptual design phase. The first step in the conceptual design phase is identifying the high-level steps of the process that will produce the desired biopharmaceutical. Examples of high-level steps are synthesis, separation, purification and conditioning. After the high-level process steps have been identified, the unit operations associated with each of the high-level steps are identified. Unit operations are discrete process steps that make up the high-level process steps. In a microbial fermentation process, for example, the high-level step of synthesis may include the unit operations of inoculum preparation, flask growth, seed fermentation and production fermentation.

The unit operation level production process is typically designed by hand and is prone to errors and inefficiencies. Often, in the conceptual design phase, the specifications for the final production process are not complete. Therefore some of the equipment design parameters, unit operation yields and actual production rates for the various unit operations must be estimated. These factors introduce errors into the initial design base of the production process. Additionally, since the production process is designed by hand, attempting to optimize the process for efficiency and production of biopharmaceutical products is impractically time consuming.

Scale calculations for each of the unit operations are performed to determine the size and capacity of the equipment necessary to produce the desired amount of product per batch. Included in the scale calculations is the number of batches per year needed to produce the required amount of biopharmaceutical product. A batch is a single run of the biopharmaceutical process that produces the product. Increasing the size and capacity of the equipment increases the amount of product produced per batch. The batch cycle time is the amount of time required to produce one batch of product. The amount of product produced in a given amount of time, therefore, is dependent upon the amount produced per

batch, and the batch cycle time. The scale calculations are usually executed by hand to determine the size and capacity of the equipment that will be required in each of the unit operations. Since the scale calculations are developed from the original conceptual design parameters, they are also subject to the same errors inherent in the initial conceptual design base.

Typically a process flow diagram is generated after the scale calculations for the unit operations have been performed. The process flow diagram graphically illustrates the process equipment such as tanks and pumps necessary to accommodate the process for a given batch scale. The process flow diagram illustrates the different streams of product and materials through the different unit operations. Generally associated with the process flow diagram is a material balance table which shows the quantities of materials consumed and produced in each step of the biopharmaceutical production process. The material balance table typically includes rate information of consumption of raw materials and production of product. The process flow diagram and material balance table provides much of the information necessary to develop a preliminary equipment list. The preliminary equipment list shows the equipment necessary to carry out all of the unit operations in the manufacturing procedure. Since the process flow diagram, material balance table and preliminary equipment list are determined from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base.

A preliminary facility layout for the plant is developed from the process flow diagram, material balance table and preliminary equipment list. The preliminary facility layout usually begins with a bubble or block diagram of the plant that illustrates the adjacencies of rooms housing different high-level steps, as well as a space program which dimensions out the space and square footage of the building. From this information a preliminary equipment layout for the plant is prepared. The preliminary equipment layout attempts to show all the rooms in the plant, including corridors, staircases, etc. Mechanical, electrical and plumbing engineers estimate the mechanical, electrical and plumbing needs of the facility

based on the facility design layout and the utility requirements of the manufacturing equipment. Since the preliminary facility layout is developed from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base.

Typically the next phase of biopharmaceutical plant design is preliminary piping and instrumentation diagram (P&ID) design. Preliminary P&IS are based on the process flow diagram from the conceptual design phase. Often the calculations on the process design are re-run and incorporated into the preliminary P&ID. The preliminary P&IS incorporate the information from the material balance table with the preliminary equipment list to show the basic piping and instrumentation required to run the manufacturing process

Detailed design is the next phase of biopharmaceutical plant design. Plans and specifications which allow vendors and contractors to bid on portions of the biopharmaceutical plant are developed during the detailed design. Detailed P&IS are developed which schematically represent every detail of the process systems for the biopharmaceutical plant. The detailed P&IS include for example, the size and components of process piping, mechanical, electrical and plumbing systems; all tanks, instrumentation, controls and hardware. A bill of materials and detailed specification sheets on all of the equipment and systems are developed from the P&IS. Detailed facility architecture diagrams are developed that coincide with the detailed P&IS and equipment specifications. The detailed P&IS and facility construction diagrams allow builders and engineering companies to bid on the biopharmaceutical plant project. Since the preliminary and detailed P&IS are developed from the original conceptual design parameters, they are subject to the same errors inherent in the initial conceptual design base. Reworking the preliminary and detailed P&IS due to errors in the conceptual design phase can cost thousands of dollars per diagram.

The inability to accurately model and simulate the biopharmaceutical production process drives inaccurate initial design. Often, these inaccuracies result in changes to the design and construction diagrams at the plant construction

site, or repair and reconstruction of the plant during the construction phase resulting in millions of dollars in additional cost.

Solution preparation is one of the primary consumers of capital and utility resources in the construction and operation of a biopharmaceutical facility. Often, the facility and process designers specify equipment that is many times what is required to support their solution preparation needs in order to ensure that all of the processes in the facility can be supported. Equipment, utility and cleaning equipment costs are a function by the preparation and use of solutions. The excess capacity, therefore, results in wasted construction capital and continuous losses during the operation of the plant.

What is needed, therefore, is a system and method for accurately simulating, modeling and scheduling solution preparation in the biopharmaceutical production process. A method and system for simulating, modeling and scheduling solution preparation in the biopharmaceutical production process would allow designers to reduce the number of errors introduced into plant design at the earliest stages. Such a system and method would also allow an engineer to validate the production process design and maximize the efficiency of the plant by finding optimum equipment configurations. Such a system and method would allow the generation of detailed specifications for the equipment and solution preparation scheduling that would smooth the transition throughout all of the design phases and fix the cost of design and construction of a biopharmaceutical facility.

### ***Summary of the Invention***

The present invention satisfies the above-stated needs by providing a method and system for simulating, modeling and scheduling solution preparation in the biopharmaceutical production process. The system and method includes the steps of identifying a solution for preparation and its associated volume. After the solution for preparation is identified, a predetermined start date and one successive

start date for solution preparation for the solution are identified. After the solution, start and successive start dates are identified, the solution is assigned to a preparation vessel. After the solution has been assigned to a preparation vessel, the duration of the solution preparation procedure is determined and assigned to the solution preparation vessel.

### ***Brief Description of the Figures***

FIG. 1 illustrates a flow diagram of the process to generate a block flow diagram and a process time line according to the present invention.

FIG. 2 illustrates a flow diagram of the process for determining the necessary reactor volume according to the present invention

FIG. 3 illustrates a unit operation list for a microbial fermentation process.

FIG. 4 illustrates a unit operation list for a mammalian cell culture process.

FIG. 5 illustrates a flow diagram for cross-referencing a unit operation list with a process parameters table according to the present invention.

FIG. 6 illustrates an exemplary process parameters table.

FIG. 7 illustrates the process for generating a block flow diagram according to the present invention.

FIG. 8 illustrates an exemplary block flow diagram according to the present invention.

FIG. 9 illustrates a block flow diagram for the process of generating a process time line according to the present invention.

FIGS. 10-11 illustrate a high-level process time line according to the present invention.

5                   FIGS. 12A-12H illustrate a detailed process time line according to the present invention.

FIG. 13 is a block flow diagram illustrating an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process.

10                   FIG. 14 is a block flow diagram illustrating the step of determining the solution preparation time associated with each solution preparation vessel.

FIG. 15 illustrates an exemplary list of solution preparation parameters.

15                   FIG. 16 is a block flow diagram illustrating the step of assigning the solutions required by the biopharmaceutical production process to particular solution preparation vessels.

FIG. 17 illustrates an exemplary list of solution preparation procedure parameters.

FIG. 18 illustrates an exemplary preparation vessel to solution assignment list.

20                   FIG. 19 illustrates an exemplary computer according to an embodiment of the present invention.

FIG. 20 is a block flow diagram illustrating the step of determining the calculated preparation start date and next solution preparation date for each solution

FIG. 21 illustrates an exemplary master quality control protocol table.

5           FIG. 22 is a block flow diagram illustrating the step of generating a solution preparation equipment quality control time line.

FIG. 23 is a block flow diagram illustrating the step of generating a preparation equipment quality control time line

10           FIG. 24 is a block flow diagram illustrating the step of determining the earliest solution preparation start date for each solution preparation vessel.

FIG. 25 is a block flow diagram illustrating the step of determining the latest solution preparation start date for each solution preparation vessel.

FIG. 26 is a block flow diagram illustrating the step of calculating solution preparation vessel utilization time.

15           FIG. 27 is a block flow diagram illustrating the step of calculating the cumulative solution preparation time for each solution preparation vessel.

FIG. 28 is a block flow diagram illustrating the step of determining the percentage utilization of each solution preparation vessel.

20           FIG. 29 is a block flow diagram illustrating the step of generating an initial solution prep shift schedule.

FIG. 30 is a block flow diagram illustrating the step of back scheduling solution preparation in the initial solution prep shift schedule.

FIG. 31 illustrates an exemplary initial solution preparation shift schedule.

FIG. 32 is a block flow diagram illustrating the process for generating a solution preparation schedule.

FIG. 33 is a block flow diagram illustrating an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process.

FIG. 34 is a block flow diagram illustrating the step of generating the preparation equipment protocol table.

FIG. 35 is a block flow diagram illustrating the step of generating the equipment preparation procedure table.

FIGS. 36A-36H illustrate exemplary preparation equipment protocol tables.

FIGS. 37A-37B illustrate an exemplary equipment preparation procedure table

FIG. 38 is a block flow diagram illustrating the step of generating the equipment dimension table.

FIG. 39 illustrates an exemplary equipment dimension table.



FIG. 40 is a block flow diagram illustrating the step of generating the master list of equipment requiring preparation.

FIG. 41 is a block flow diagram illustrating the step of generating the equipment preparation load table.

5                   FIGS. 42A-42D illustrate an exemplary equipment preparation load table.

FIG. 43 is a block flow diagram illustrating the step of generating the equipment preparation load summary table.

FIG. 44 is a block flow diagram illustrating the step of determining the capacities of the preparation equipment.

10                   FIGS. 45A-45I illustrate an exemplary process equipment quality control assay sample time line.

FIG. 46 is a block flow diagram illustrating the step of generating the equipment preparation time line

15                   FIG. 47 is a block flow diagram illustrating the step of generating the preparation equipment list with functional specification and costs.

FIG. 48 is a block flow diagram illustrating the step of generating the preparation equipment utility time line.

FIG. 49 is a block flow diagram illustrating the step of generating a process equipment maintenance table.

FIG. 50 is a block flow diagram illustrating the step of generating a process equipment maintenance time line.

FIG. 51 is a block flow diagram illustrating the step of generating a solution preparation equipment maintenance table.

5           FIG. 52 is a block flow diagram illustrating the step of generating a solution preparation equipment maintenance time line

FIG. 53 is a block flow diagram illustrating the step of generating a preparation equipment maintenance table.

10           FIG. 54 is a block flow diagram illustrating the step of generating a preparation equipment maintenance time line.

FIG. 55 is a block flow diagram illustrating the step of generating a process equipment calibration table.

FIG. 56 is a block flow diagram illustrating the step of generating a process equipment calibration time line.

15           FIG. 57 is a block flow diagram illustrating the step of generating a solution preparation equipment calibration table

FIG. 58 is a block flow diagram illustrating the step of generating a solution preparation equipment calibration time line.

20           FIG. 59 is a block flow diagram illustrating the step of generating a preparation equipment calibration table.

FIG 60 is a block flow diagram illustrating the step of generating a preparation equipment calibration time line.

FIG. 61 is a block flow diagram illustrating the step of generating a master quality control protocol table

5                   FIG 62 is a block flow diagram illustrating the step of generating a master quality control sample table.

FIG. 63 is a block flow diagram illustrating the step of generating a process equipment quality control time line.

10                   FIGS. 64A-64AB illustrate an exemplary process equipment maintenance time line

Appendix A1-A7 is a detailed example of a process parameters table showing a list of unit operations and their associated parameters

## ***Detailed Description of the Preferred Embodiments***

### ***1.0 Biopharmaceutical Batch Process Simulator***

15                   FIG. 1 illustrates a high-level flow diagram of the preferred embodiment. The process begins by determining the necessary reactor vessel capacity at step 102. The reactor vessel is the container in which the crude product is first synthesized. For example, in mammalian cell culture processes, the reactor vessel houses the mammalian cells suspended in growth media. Next, the unit operation  
20                   sequence for production of the biopharmaceutical product is determined at step 104. The unit operation sequence is the series of unit operations that are required to produce the biopharmaceutical product. Each unit operation is an individual

step in the biopharmaceutical manufacturing process with an associated set of manufacturing equipment. The unit operation list is the list of unit operations that make up the unit operation sequence and their associated sequence information. The unit operation sequence information is the information that defines the scheduling cycles for each of the unit operations in the unit operation list. Scheduling cycles are iterations ((the default being one (1)) of unit operations in the unit operation sequence. Together, the unit operation list and the unit operation sequence information define the unit operation sequence. The desired biopharmaceutical product dictates the particular unit operations and their order in the biopharmaceutical production process. Some examples of unit operations are: inoculum preparation, initial seeding of the reactor vessel, solids harvest by centrifugation, high-pressure homogenization, dilution, etc.

Scheduling cycles and cycle offset duration for each of the unit operations in the biopharmaceutical production process are determined at step 106. Scheduling cycles are iterations of unit operations in the unit operation sequence, and occur in three levels. Additionally, each level of scheduling cycle has an associated offset duration that dictates the time period between the beginnings successive scheduling cycles.

"Cycles per unit operation" is the first level of scheduling cycles. Cycles per unit operation are defined as the number of iterations a unit operation is repeated in a process by itself before proceeding to the next operation. For example, the harvest and feed unit operation in a mammalian cell culture process has multiple cycles per unit operation. Product-rich media is drawn from the reactor vessel and nutrient-rich media is fed into the reactor vessel multiple times during one harvest and feed unit operation. The multiple draws of product-rich reactor media are pooled for processing in the next unit operation.

The second level of scheduling cycles is "cycles per batch." Cycles per batch are defined as the number of iterations a set of consecutive unit operations are repeated as a group before proceeding to the next unit operation after the set of consecutive unit operations. The set of consecutive unit operations repeated

as a group are also referred to as a subprocess. For example, the set of unit operations including inoculum preparation, flask growth, seed fermentation, production fermentation, heat exchange, and continuous centrifugation/whole-cell harvest in a microbial fermentation process are often cycled together. Running through each of the six steps results in a single harvest from the microbial fermentation reactor vessel. Multiple harvests from a reactor vessel may be needed to achieve a batch of sufficient quantity. Each additional harvest is pooled with the previous harvest, resulting in a single batch of cell culture for the process.

The third level of scheduling cycles is "cycles per process." Cycles per process are defined as the number of iterations a batch cycle is repeated for a process that employs continuous or semi-continuous product synthesis. In such a case, a single biopharmaceutical production process may result in multiple batches of product. For example, in a mammalian cell-culture process a single cell culture is typically in continuous production for 60-90 days. During this period multiple harvests of crude product are collected and pooled on a batch basis to be processed into the end product biopharmaceutical. The pooling of multiple harvests into a batch of material will occur several times during the cell culture period resulting in multiple batch cycles per process.

In step 108, a process parameters table master list is referenced to obtain all operational parameters for each unit operation in the unit operation list. The process parameters table contains a list of all unit operations and operational parameters necessary to simulate a particular unit operation. Examples of operational parameters are the solutions involved in a particular unit operation, temperature, pressure, duration, agitation, scaling volume, etc. Additionally, the process parameters table supplies all of the individual tasks and task durations involved in a particular unit operation. For example, the unit operation of inoculum preparation includes the individual tasks of setup, pre-incubation, incubation, and cleanup. Examples of unit operations for biopharmaceutical manufacturing and their associated operational parameters are included in this application as Appendix A1-A7.

A block flow diagram is generated at step 110 after unit operation list has obtained the operational parameters from the process parameters table at step 108. The block flow diagram illustrates each unit operation in the manufacturing process as a block with inputs for both incoming product and new material, as well as outputs for both processed product and waste. The block flow diagram is a simple yet convenient tool for quantifying material flows through the process in a way that allows the sizing of many key pieces of equipment relative to a given process scale.

The information in each block of the block flow diagram is generated from the parameters and sizing ratios from the process parameters table in the unit operation list, and block flow diagram calculation sets. A calculation set is a set of algebraic equations. The parameters and calculation sets are used to calculate the quantities of material inputs, product and waste outputs required for that unit operation based on the quantity of product material being received from the previous unit operation. Likewise, a given block flow diagram block calculates the quantity of product to be transferred to the next unit operation block in the manufacturing procedure. These calculations take into account the unit operation scheduling cycles identified at step 106, as further explained below.

A process time line is generated at step 112 after the block flow diagram is generated at step 110. The process time line is a very useful feature of the present invention. The process time line is generated from the unit operation list, the tasks associated with each of the unit operations, the scheduling cycles for each of the unit operations in the process, the process parameters from the master process parameters table and the volume of the material as calculated from the block flow diagram. The process time line is a relative time line in hours and minutes from the start date of the production process. The relative time is converted into days and hours to provide a time line for the beginning and ending times of each unit operation and its associated tasks for the entire biopharmaceutical drug production process.

The process time line is a very powerful tool for process design. The process time line can be used to accurately size pumps, filters and heat exchangers used in unit operations, by calculating the flow rate from the known transfer time and the volume of the material to be transferred, filtered or cooled. The process time line accurately predicts loads for labor, solution preparation, equipment cleaning, reagent, process utilities, preventative maintenance, quality control testing, etc.

FIG. 2 further illustrates step 102 of determining the necessary reactor vessel capacity. The amount of biopharmaceutical product to be produced in a given amount of time is determined in step 202. Normally, the amount of biopharmaceutical product required is expressed in terms of mass produced per year. The number of reactor vessel runs for a particular biopharmaceutical product per year is determined at step 204. Factors considered when determining the number of reactor vessel cycles for a particular biopharmaceutical product are, for example, the number of biopharmaceutical products produced in the reactor vessel (i.e., the reactor vessel is shared to produce different products), the reaction time for each cycle of the reactor vessel and the percentage of up-time for the reactor vessel over the year.

The yield of each batch or reactor cycle is calculated at step 206. The yield from each batch or a reactor cycle is process-dependent and is usually expressed in grams of crude product per liter of broth. Given the required amount of biopharmaceutical product per year from step 202, the number of reactor cycles available to produce the required biopharmaceutical product from step 204, and the yield of each reactor cycle from step 206, the necessary reactor volume to produce the required amount of biopharmaceutical product is calculated at step 208.

FIG. 3 illustrates a unit operation list for an exemplary microbial fermentation biopharmaceutical production process. The far left-hand column, column 302, lists the unit operation sequence numbers for each of the unit operations in the process. The exemplary microbial fermentation unit operation

list includes 23 unit operations. The unit operation sequence number defines the order in which the unit operations occur. For example, unit operation sequence number 1, inoculum preparation, occurs first, before unit operation sequence number 2, flask growth. Column 304 shows the unit operation identifier codes associated with each of the unit operations in the unit operation list (see step 108). The unit operation identifier codes are used to bring operational parameters from the process parameters table into the unit operation list. For example, heat exchange, unit operation list numbers 5, 8 and 10, has a unit operation identifier code 51.

As described above with reference to FIG. 1, after the unit operation sequence for a particular biopharmaceutical production process has been determined at step 104, the scheduling cycles associated with each unit operation is determined at step 106. Columns 306, 310 and 318 list the number of scheduling cycles for the microbial fermentation process of FIG. 3. Scheduling cycles are iterations of unit operations in the unit operation sequence, and occur in three levels. Additionally, each level of scheduling cycle has an associated offset duration that dictates the time period between the beginnings of successive scheduling cycles, shown in columns 308, 316 and 324.

Column 306 lists the number of cycles per unit operation for each of the unit operations in the microbial fermentation unit operation sequence. In the exemplary microbial fermentation unit operation sequence, each of the unit operations has only one cycle per unit operation. Again, cycles per unit operation define the number of iterations a unit operation is repeated in a process by itself before proceeding to the next unit operation.

Column 308 lists the cycle offset duration in hours for the cycles per unit operation. Since each of the unit operations in the microbial fermentation example of FIG. 3 has only one cycle per unit operation, there is no cycle offset duration for any of the unit operations. Cycle offset duration defines the time period between the beginnings of successive scheduling cycles.



Column 310 lists the cycles per batch for each of the unit operations in the microbial fermentation unit operation sequence. Unit operation sequence numbers 1-6 are defined as having three cycles per batch. Cycles per batch defines the number of iterations a set of consecutive unit operations are repeated as a group before proceeding to the next unit operation. In FIG. 3, for example, the set of unit operations 1-6, as defined in unit operation start column 312 and unit operation end column 314, cycle together as a group (e.g., the sequence of unit operations for the exemplary microbial fermentation process is 1, 2, 3, 4, 5, 6, 1, 2, 3, 4, 5, 6, 1, 2, 3, 4, 5, 6 and 7). Unit operations 1-6 cycle together as a group three times before the process continues to unit operation 7, as defined in column 310.

After unit operation sequence numbers 1-6 have cycled consecutively three times, the microbial fermentation production process continues at unit operation sequence number 7, resuspension of cell paste. After unit operation sequence number 7, the process continues with three cycles per batch of unit operation sequence numbers 8-10. The unit operations of heat exchange, cell disruption and heat exchange are cycled consecutively three times, as defined in columns 310, 312 and 314. After unit operation sequence numbers 8-10 have cycled three times, the microbial fermentation production process continues at resuspension/surfactant, unit operation sequence number 11.

Unit operation sequence numbers 11 and 12 cycle together two times, as defined by columns 310, 312 and 314. After unit operation sequence numbers 11 and 12 have been cycled two times, the microbial fermentation production process continues without cycling from unit operation sequence number 13 through unit operation sequence number 23 to conclude the microbial fermentation production process.

Columns 326-332 of FIG. 3 represent the step wise recover (SWR) and overall recovery (OAR) percentages of the product and total proteins. SWR is the recovery of protein for the individual unit operation for which it is listed. OAR is the recovery of protein for the overall process up to and including the unit

operation for which it is listed. The product recovery columns represent the recovery of the desired product protein from the solution in the process. The protein recovery columns represent the recovery of contaminant proteins from the solution which result in higher purity of the product solution.

FIG. 4 illustrates a unit operation list for an exemplary mammalian cell culture production process. Column 402 lists unit operation sequence numbers 1-19. Unit operation sequence numbers 1-19 define the order in which the unit operations of the mammalian cell culture production process occur. The most notable differences between the microbial fermentation process of FIG. 3 and the mammalian cell culture process of FIG. 4 are the multiple cycles per unit operation of unit operation sequence number 8 and the multiple cycles per process of unit operation sequence numbers 8-18

Unit operation sequence number 8 of FIG. 4 illustrates the concept of multiple cycles per unit operation. Unit operation sequence number 8 is the unit operation of harvesting product rich growth media from and feeding fresh growth media into the mammalian cell reactor vessel. In most mammalian cell culture processes, the product is secreted by the cells into the surrounding growth media in the reactor vessel. To harvest the product, some of the product rich growth media is harvested from the reactor vessel to be processed to remove the product, and an equal amount of fresh growth media is fed into the reactor vessel to sustain production in the reactor vessel. The process of harvesting and feeding the reactor vessel can continue for many weeks for a single biopharmaceutical production process. Unit operation sequence number 8 is repeated seven times, or 7 cycles per unit operation (e.g., the unit operation sequence is 7, 8, 8, 8, 8, 8, 8, 9). Note that the offset duration for unit operation sequence number 8 is 24 hours. The offset duration defines the time period between the cycles per unit operation. In the example of FIG. 4, unit operation sequence number 8 is repeated 7 times (7 cycles per unit operation) and each cycle is separated from the next by 24 hours, or one day. This corresponds to unit operation sequence number 8 having a duration of one week, with a harvest/feed step occurring each day.

FIG. 4 also illustrates the feature of multiple cycles per process. Cycles per process is defined as the number of iterations a batch cycle is repeated in a given process that employs continuous or semi-continuous product synthesis. Each batch cycle results in a batch of product. A single biopharmaceutical production process, therefore, may result in multiple batches of product. In the mammalian cell culture process example of FIG. 4, unit operation sequence numbers 8-18 are repeated together as a group eight times (column 418). Each of these cycles of unit operation sequence numbers 8-18 produce one batch of product (columns 420-422). The offset between each cycle of unit operation sequence numbers 8-18 is 168 hours, or one week (column 424).

In the example of FIG. 4, unit operation sequence numbers 8-18 proceed as follows: the reactor vessel is harvested and fed once each day for seven days; the results of the harvest/feed operation are pooled in unit operation sequence number 9 at the end of the seven days; unit operations 9-18 are then executed to process the pooled harvested growth media from unit operation sequence number 8. Unit operation sequence numbers 8-18 are cycled sequentially once each week to process an additional seven day batch of harvested growth media from unit operation sequence number 8. At the end of eight weeks, the mammalian cell culture process is completed.

FIG. 5 further illustrates step 108, cross referencing the unit operation sequence with the master process parameters table. The operational parameters in the process parameters table are those parameters necessary to simulate a particular unit operation. The parameters from the process parameters table define the key operational parameters and equipment sizing ratios for each unit operation in the unit operation sequence. The values for these parameters and ratios are variables which can be easily manipulated and ordered to model and evaluate alternative design scenarios for a given process scale. Examples of the process parameters associated with each unit operation are listed in Appendix A1-A7. It should be noted, however, that the list of unit operations, parameters, values, and scaling ratios is not exhaustive. One of ordinary skill in the art could

expand the process parameters table to encompass additional unit operations and production processes for other batch process industries such as chemical pharmaceutical, specialty chemical, food, beverage and cosmetics. Such expansion would allow the present invention to simulate and schedule additional batch production processes for other such batch processes.

FIG. 5 illustrates the files necessary to cross-reference the unit operation list with the process parameters table in step 108. Exemplary unit operation list 502 for the biopharmaceutical production process and process parameters table 504 are input into processing step 506. Step 506 cross-references the unit operation list and process parameters table based on unit operation identification code (see FIG. 3). The parameters are copied from the process parameters table 504 into the unit operation list 502 to generate unit operation list 508.

FIG. 6 further illustrates exemplary process parameters table, 504. The operational parameters in the process parameters table are those parameters necessary to simulate a particular unit operation. The unit operation identification codes of process parameters table 504 are used in the cross-reference step 506 to assign the parameters from the process parameters table 504 to the unit operation list 502. Examples of operational parameters are the solutions involved in a particular unit operation, temperature, pressure, duration, agitation, scaling volume, etc. Additionally, the process parameters table defines all of the individual tasks and task durations involved in each unit operation. It should be noted, however, one of ordinary skill in the art could expand the process parameters table to encompass additional unit operations and production processes for other batch process industries such as chemical pharmaceutical, specialty chemical, food, beverage and cosmetics. Such expansion would allow the present invention to simulate and schedule additional batch production processes for other such batch processes.

FIG. 7 further illustrates step 110, generating a block flow diagram. A block flow diagram depicts each unit operation in the biopharmaceutical production process as a block with inputs for both incoming product and new

material, as well as outputs for both processed product and waste. The material that flows through each of the unit operation blocks is quantified by calculation sets in each of the block flow diagram blocks. A unit operation block in a block flow diagram is a graphical representation of a unit operation. A calculation set is a set of algebraic equations describing a unit operation. Some examples of outputs of the calculation sets are: required process materials for that unit operation, equipment performance specifications and process data outputs to be used for the next unit operation. Some examples of inputs to the calculation sets are: product quantity (mass) or volume (liters) from a previous unit operation, other parameters and/or multipliers derived from the process parameters table, as well as the design cycles defined in the unit operation list.

Block flow diagram 708 is generated from unit operation list 508 and block flow diagram calculation set 704. Block flow diagram calculation set 704 is an exhaustive list of unit operation identifier codes and the calculation sets associated with each unit operation identifier. Unit operation list 508 and block flow diagram calculation set 704 are linked together based on unit operation identifier code.

Step 706 calculates the block flow diagram material flow requirements and basic equipment sizing requirements from unit operation list 508 which includes all of the associated operational parameters from the process parameters table, and the block flow diagram calculation set 704. Block flow diagram 708 allows the sizing of many key pieces of equipment relative to a given process scale. Since the material flow quantities into and out of each unit operation is determined at step 706, the capacity of many equipment items involved in each unit operation can be determined. The block flow diagram also manages important information in the unit operation list 502 such as the percent recovery, percent purity and purification factor of the product in each unit operation. This information helps identify the steps in the process that may need optimization.

The following is an example calculation set for a tangential flow micro-filtration (TFMF) system unit operation. Tangential flow micro-filtration is an

important process technology in biopharmaceutical manufacturing. This technology significantly extends the life of the filtration media and reduces the replacement cost of expensive filters.

TFMF generically requires the same steps to prepare the membrane for each use as well as for storage after use. The design parameters for each unit operation such as TFMF have been developed around these generic design requirements.

***Generic Parameters (Variables) from the Process Parameters Table***

Equipment Design Type	Plate & Frame
Membrane Porosity	0.2 micron
Membrane Flux rate	125 Liters/square meter/hour
Process Time	2 Hours
Retentate/Filtrate Rate	20 to 1
Flush volume	21.5 Liters/square meter
Prime volume	21.5 Liters/square meter
Wash Volume	0.5 % of Process Volume
Regenerate Volume	10.8 Liters/square meter
Storage Volume	21.5 Liters/square meter
% Recovery of Product	95%
% Recovery of Total Protein	80%
Clean In Place (CIP)	Yes
Steam In Place (CIP)	Yes

***Input Values from Previous Unit Operation***

Product Volume	1,000 Liters
Product Quantity	1.5 Kg
Total Protein Quantity	3 0 Kg

- 5            The calculation set for this unit operation first takes the incoming process volume and uses it as a basis of sizing the filtration membrane for the filtration system based on the above flux rate and required processing time.

$$1,000 \text{ Liters} / 125 \text{ L/SM/Hr} / 2 \text{ Hours} = 4.0 \text{ SM of 0.2 micron membrane}$$

- 10           After calculating the square meter (SM) of membrane required by this unit operation, the volumes of each of the support solutions can be calculated based on the above volume ratios.

15	Flush volume	21.5 Liters/SM x 4.0 SM = 86 Liters
	Prime volume	21.5 Liters/SM x 4.0 SM = 86 Liters
	Wash Volume	5 % of 1,000 Liters = 50 Liters
	Regenerate	21.5 Liters/SM x 4.0 SM = 86 Liters
	Storage	10.8 Liters /SM x 4.0 SM = 42 Liters

The flow rate of the filtrate is calculated from the volume to be filtered and the required process time

$$1,000 \text{ Liters} / 2 \text{ Hours} = 8.3 \text{ Liters/minute}$$

- 20           The flow rate of the retentate is calculated based on the above retentate/filtrate ratio.

$$8.3 \text{ Liters per minute} \times 20 = 167 \text{ Liters/minute}$$

Based on the input of the process volume to this unit operation and the above parameters, the equipment size, the filtration apparatus, the retentate pump, the support linkage and associated systems can be designed.

In addition, the input values for the quantity of product and contaminant protein received from the previous unit operation together with the recovery factors listed in the parameters allow the calculation of the cumulative recovery of product through this step, as well the percent purity of the product and the product purification factor for this step. This information is helpful for identifying steps in the manufacturing process which require optimization.

FIG. 8 illustrates an exemplary block flow diagram for the first five unit operations of the microbial fermentation process unit operation list of FIG. 3. Unit operations 1 through 5 are shown as blocks 802, 804, 806, 808 and 810. The input solutions to each of the steps are shown as arrows tagged with solution identifier information from the unit operation list 508. The process streams to which these solutions are added at each unit operation are also shown as arrows tagged with process stream identifier information. Working from the initial process stream characteristics (P-101) in unit operation 1, inoculum prep, the volumes of input materials (solutions) and subsequent process streams in each of the unit operations is determined using scale-up ratios which are included in the information from the unit operation list 508 for each respective unit operation. For example, the volume of solutions and process streams flowing into and out of each of unit operation blocks 802-810 in FIG. 8 is determined by the initial starting characteristics of the process stream P-101 and the volume of its associated input material S-101 in the first unit operation, block 802 and the scale up ratio in each of the successive unit operations, blocks 804-810. The solutions involved in each of unit operation blocks 802-810 are likewise part of the information for each respective unit operation in the unit operation list 508.



FIG. 9 further illustrates step 112, generating the process time line. The process time line is generated (steps 904-906) from unit operation list 508 and block flow diagram calculation set 704. Unit operation list 508 contains enough input information to generate a detailed process time line which includes the start and stop times for most of the tasks associated with each unit operation. The durations of some unit operation tasks are not scale dependent. The durations of other unit operation tasks are, however, scale dependent. In the latter case, as a process is scaled up, the amount of time required to complete a unit operation task increases. In such cases, where duration of a unit operation task is scale dependent, block flow diagram calculation set 704 is required to calculate the quantity of material handled by the unit operation task. After the quantity of material handled by a unit operation task is determined, its duration can be determined. Examples of scale dependent task durations are the time required to pump solutions from one storage tank to another, the amount of time required to heat or cool solutions in a heat exchanger, the amount of time required to filter product or contaminants from solution

FIG. 10 is an example of a high-level process time line for a microbial fermentation process. The unit operation sequence of the process time line of FIG. 10 corresponds to the unit operation list of FIG. 3. The high-level process time line shown in FIG. 10 illustrates two process cycles of the microbial fermentation unit operation sequence, labeled "First Process Cycle" and "Second Process Cycle." A process cycle is a complete run of the biopharmaceutical production process, as defined by the unit operation sequence for the process.

The first two columns of the process time line of FIG. 10 identify the unit operation sequence number and unit operation description of the unit operation being performed, respectively. The first three sets of unit operations correspond to the three cycles per batch of unit operation sequence numbers 1-6 of FIG. 3. Three cycles of unit operations 1-6 are performed and the results are pooled into unit operation 7, pool harvests. The two columns to the right of the duration

column identify the week and day that the particular unit operation is occurring in the first process cycle.

The day and the week each unit operation is performed is calculated from the start time of the process, as well as the cumulative duration of each of the previous unit operations. In the example of FIG. 10, Sunday is defined as the first day of the week. In the example of FIG. 10, the process sequence begins at unit operation 1, inoculum prep, on Friday of the first week. After unit operation 1 has completed (24 hours later, since unit operation 1 has a 24 hour duration) unit operation 2 is performed on Saturday. The begin and end times for each successive unit operation are calculated from the duration of the unit operation and end time of the previous unit operation. Note that FIG. 10 is calculated to the day and week only for the purposes of explanation. Usually the process time line is determined for each of the tasks associated with a unit operation to the minute.

As illustrated in FIG. 10, unit operation 7 occurs on Monday of the third week in the first process cycle. The third column from the left is the duration of each of the unit operations. After the three cycles of unit operations 1 through 6 have been pooled in unit operation 7, the process continues at unit operations 8 through 10, heat exchange, cell disruption and heat exchange. Each of unit operations 8 through 10 are cycled three times and the associated scheduling information is contained in column to the right of the unit operation duration. Since each cycle of unit operations 8 through 10 have a duration of .5 hours, as shown in column 3, each cycle occurs on Monday of the third week in the process.

FIG. 11 illustrates the final unit operations of the process time line for the microbial fermentation process. After 3 cycles of unit operations 8 through 10 have been completed, unit operation sequence numbers 11 and 12 cycle together two times on Monday, week 3 of the first process cycle. After unit operation sequence numbers 11 and 12 have been cycled twice, the microbial fermentation production process continues without cycling from unit operation sequence number 13 through unit operation sequence number 22 to conclude the microbial

fermentation production process. The durations and associated start times are listed for each of the unit operations 13-22.

FIGS. 12A-12H illustrate the preferred embodiment of a detailed process time line. The unit operation sequence of the process time line of FIGS. 12A-12H correspond to the unit operation list of FIG. 3. The process time line of FIGS. 12A-12H illustrates a single process cycle of the microbial fermentation unit operation sequence. The individual tasks associated with each unit operation are included after the unit operation. For example, in FIG. 12A, unit operation 1A, inoculum prep, consists of the individual tasks of set up, pre-incubation, incubation, and clean up. Columns 11-14 show the start date and time and finish date and time for each of the tasks in each unit operation. Since setup and clean up are not part of the critical path of the process, they do not directly affect the start and end times of following unit operations. The start and finish date and times for the set up and clean up operations of each of the unit operations are valuable because they ensure that the equipment will be available for each unit operation if the process time line is followed.

The process time line of FIGS. 12A-12H includes examples of unit operation task duration calculations. Row 20, column 15 of FIG. 12A, which corresponds to the harvest task of unit operation 3A, seed fermentation, is an example of a duration calculation. As stated above, the duration of some unit operations is process scale dependent (i.e., the duration is dependent upon the volume processed). The harvest task in the seed fermentation unit operation is an example of a task whose duration is process scale dependent. In column 15, the calculations column, information listed for the harvest task is 50 liters, 1.7 liters/minute (LPM), and 0.5 hours. Fifty liters represents the volume of material that is harvested during a harvest task. 1.7 liters/minute represents the rate at which the solution is harvested. Given the volume to be harvested and the flow rate of the harvest, the duration of the harvest task is calculated to be 0.5 hours. Each task in a unit operation that is volume dependent has its duration calculated in order to generate the process time line of FIGS 12A-12H.

The process time line of FIGS. 12A-12H can be resolved to minutes and seconds, if necessary. The accuracy of the process time line allows the precise planning and scheduling of many aspects of the batch manufacturing process. The process time line scheduling information can be used to schedule manufacturing resources such as labor, reagents, reusables, disposables, etc., required directly by the manufacturing process. Pre-process support activities such as solution preparation, and equipment prep and sterilization, required to support the core process, including the labor, reagents, etc. can be scheduled, cost forecasted and provided for. Post-process support activities such as product formulation, aseptic fill, freeze drying, vial capping, vial labeling and packaging required to ship the purified product in a form ready for use may be added to the process time line and managed. Based on the process time line, labor, reagents, etc., required to support these post-process support functions can be acquired and managed. One of the most important aspects of the present invention is the determination of process utility loads such as USP Purified Water, Water For Injection, Pure Steam, etc., for all of the manufacturing equipment. The process time line can be used to determine the peak utility loading, and utility requirements for the facility. Building utility loads such as building steam, heating, ventilation, air conditioning, plumbing, etc., for all manufacturing equipment, process areas and facility equipment can be determined based on the process time line and the equipment associated with each of the unit operations. The process time line can be used to measure the time that the equipment has been in service to schedule preventative maintenance of all plant equipment, Quality Assurance activities including instrument calibration, automated batch documentation, etc. and Quality Control activities including process system maintenance, raw material testing, in process testing and final product testing, etc.

## 2.0 Solution Preparation Scheduling Module

The preferred embodiment of the present invention is a computer based system and method for the simulation, modeling and scheduling of batch process solution preparation. The preferred embodiment is based on a method for generating scheduling information which accurately defines the complex manufacturing operations of solution preparation in batch manufacturing processes. This scheduling capability system allows the definition of manufacturing costs and systems in a more detailed and accurate manner than previously possible. As a result, this invention allows the rapid and accurate evaluation of numerous batch manufacturing alternatives in order to arrive at an optimal process design early in a facility development project. In so doing the invention minimizes project cost over runs which result from inaccuracies that can carry forward from the early stages of design into construction. The invention also allows the accurate scheduling of solution preparation activities in an operating manufacturing plant, including the scheduling of resources required by solution preparation such as labor, reagents, disposables, reuseables, utilities, equipment maintenance & calibration, etc..

The object of the solution preparation scheduling module is to assign each solution to a solution preparation vessel and to generate a solution preparation schedule for each solution preparation vessel. Scheduling solution preparation in each solution preparation vessel allows the biopharmaceutical production process designer to manage, predict and optimize solution preparation vessel inventory, equipment cost, utility requirements, clean and preparation and other solution preparation associated activities

FIG. 13 is a flow chart providing an overview of the process for scheduling and simulating solution preparation in a biopharmaceutical production process. Step 1302 determines the solution preparation time for each solution preparation vessel. A solution preparation vessel is a vessel used for the preparation of solution used in the biopharmaceutical production process. In the preferred

embodiment, each type of solution preparation vessel used in the biopharmaceutical production process has an associated solution preparation time. The solution preparation time is the amount of time it takes to prepare solution in the solution preparation vessel. Preparation of one solution preparation vessel's volume of solution is called a solution preparation cycle. Each solution preparation vessel has associated solution preparation parameters. Solution preparation parameters describe the amount of time necessary to complete various steps in the solution preparation process.

Step 1304 assigns the solutions in the biopharmaceutical production process to particular solution preparation vessels. Solutions are assigned to particular vessels in order to schedule and determine the load on the solution preparation vessels. Step 1304 includes the procedure of determining the total volume of each solution needed for the biopharmaceutical production process and assigning it to a preparation vessel of the appropriate size. Large volume solutions can be prepared in smaller multiple solution preparation cycles and pooled to yield a higher volume batch of solution. Conversely, smaller volume solutions can be batch prepared in larger preparation volumes to accommodate multiple process cycles provided the shelf life of these solutions allow longer storage times.

Step 1306 determines the calculated start date and the next preparation date of each solution. The calculated start date for the preparation of a solution is the date which solution preparation should begin in order to have the solution ready for use in the biopharmaceutical process. The calculated start date takes into account the amount of time necessary to prepare the solution, and other lead time factors necessary for preparation of solution. The next preparation date is the earliest date that a solution will be prepared after its calculated start date. The next preparation date is determined by adding the periodicity of solution preparation to the calculated start date. The periodicity of solution preparation is how often each solution must be prepared in order to sustain the biopharmaceutical production process.

Step 1308 determines the earliest solution preparation date for each solution preparation vessel for a given process cycle. Since each solution has been assigned to a solution preparation vessel, and the calculated start dates for each solution have been determined, step 1308 determines the earliest calculated start date for each solution preparation vessel. The earliest calculated start date associated with a solution preparation vessel is the date which the first solution is prepared in the vessel for a given process cycle. The earliest calculated start date associated with a solution preparation vessel identifies the point in the process cycle by which the preparation vessel must be available.

Step 1310 determines the latest next preparation date for each solution preparation vessel. The latest next preparation date for each solution preparation vessel is the date that a solution preparation vessel is last used for solution preparation to support a given process cycle. Based on the solution to solution preparation vessel assignments determined in step 1304, the earliest calculated start date for each solution and the next preparation dates for each of the solutions determined in step 1306, step 1310 determines the latest next preparation date for each solution preparation vessel. The earliest calculated start date and the latest next preparation date associated with a solution preparation vessel define the usage boundaries of the solution preparation vessel in the process cycle. The loading of a solution prep vessel can be evaluated during the time between the earliest calculated start date and the latest next preparation date. In the case where the usage boundary is set by a solution which is batch prepared to accommodate multiple process cycles, the usage boundary of a tank includes these multiple process cycles. Therefore the loading on a solution preparation vessel in this instance will also account for solutions from multiple process cycles.

The duration of time between the first biopharmaceutical production process activity related to a given process and the last biopharmaceutical production process activity related to that process may be called a manufacturing cycle (i.e., multiple process cycles define a manufacturing cycle). In the case where an activity, such as the preparation of a solution, accommodates multiple

process cycles, a manufacturing cycle consists of multiple process cycles. In the case where all the activities associated with a process only accommodate one process cycle a manufacturing cycle consists of only one process cycle. Therefore manufacturing cycles may consist of one or more process cycles with their related support activities.

Step 1311 calculates the use duration for each solution preparation vessel. The use duration for each solution preparation vessel is the time that a solution preparation vessel is occupied with the preparation of solution for a manufacturing cycle. For example, when multiple solutions are assigned to a single solution preparation vessel, the use duration for the solution preparation vessel is determined based on the earliest calculated start date and the latest next preparation date for all of the solutions assigned to the solution preparation vessel. The total number of hours the solution preparation vessel is occupied can be calculated from the use duration (days) and the number of shift hours per day for the particular manufacturing cycle (e.g., single shift operation would normally be 8 hours per day).

Step 1312 calculates the cumulative solution preparation time for each solution preparation vessel. The cumulative solution preparation time is the amount of time a solution preparation vessel is occupied with the preparation of solutions in a biopharmaceutical manufacturing cycle. Step 1312 calculates the cumulative solution preparation time for each solution preparation vessel based on:

- 1) the solutions assigned to a particular vessel;
- 2) the prep vessel use duration;
- 3) the duration of a process cycle;
- 4) the number of preps of a solution per process cycle; and
- 5) solution preparation times.

For example, if five solutions are to be prepared in a particular solution preparation vessel each requiring two preparations per process cycle, process



cycle durations of seven days, solution preparation times of three hours, during a use duration of fourteen days, the cumulative solution preparation time for the solution preparation vessel would be sixty hours over a two week period.

Step 1314 determines the percent utilization of each solution preparation vessel. The percent utilization of each solution preparation vessel is the fraction of the use duration that the solution preparation vessel is actually engaged in the preparation of solution, or the cumulative solution preparation time. The percent utilization is determined based on the use duration, cumulative solution preparation time and the number of hours per solution prep shift for the process cycle. For example, if the use duration for a solution preparation vessel is fourteen days, and there are eight shift hours per day, then the solution preparation vessel has a total availability of one hundred twelve hours. If, as calculated above, the cumulative solution preparation time for the solution preparation vessel is sixty hours, then the percent utilization of the solution preparation vessel is approximately fifty-four percent. The percent utilization of each solution preparation vessel is determined in step 1314 so that the biopharmaceutical production process planner is able to gauge the level of utilization of the solution preparation equipment and make any adjustments in the solution preparation equipment pool or production cycles.

Step 1316 generates the initial shift schedule for each solution preparation vessel. The initial shift schedule is a daily schedule of solutions to be prepared in a particular solution preparation vessel. Step 1316 generates the initial shift schedule based on the calculated start date for each solution, the periodicity of solution preparation for each solution and the solution to solution preparation vessel assignment.

Step 1318 back schedules solution preparation procedures that do not fit in the shift schedule and checks for system capacity problems. Back scheduling is the process of rescheduling solution preparation cycles for previous days or time slots. The initial shift schedule is generated regardless of the number of hours a solution preparation vessel is occupied for a particular day. For example, the

initial shift schedule may have a particular solution preparation vessel scheduled for fourteen hours of solution preparation. In a biopharmaceutical production process that operates sixteen hours a day, all of the solutions scheduled for the solution preparation vessel can be accommodated. If, however, the biopharmaceutical production process operates only eight hours a day, not all of the required solutions may be prepared on the scheduled date. Step 1318 back schedules to earlier days those solution preparation cycles that cannot be completed on the initially scheduled day. The scheduling of a back scheduled solution preparation cycle into an available shift is performed according to the priority of the oldest back scheduled date for all available back scheduled solutions. The end result of step 1318 is to generate a final shift schedule for each prep vessel which assigns the appropriate solutions to that vessel and schedules out the preparation of each solution according to shift capacity, the duration of each prep assigned to that shift.

Step 1320 generates a time line for the operation of each solution prep vessel and its associated equipment according to the shift assignments in the final shift schedule and the durations associated with each solution prep step in the solution prep procedure table. Based on this time line resources requirements for labor, reagents, disposables, reusables, utilities, maintenance, etc., can be accurately scheduled

FIG. 14 further illustrates step 1302, determining the solution preparation time for each solution preparation vessel. Step 1302 begins at step 1420 determining the setup time for a solution preparation vessel. Step 1420 compares a list of solution preparation vessels 1402 that are available for use in the biopharmaceutical production process and their associated solution preparation vessel identifiers with a master list of solution preparation vessel identifiers and their associated set up times 1410. Solution identifiers and solution preparation vessel identifiers are keys or tags that identify individual solution preparation vessel and solution types. Examples of solution preparation vessel set up times are illustrated in FIG. 15, column 1410. List of solution preparation vessels 1402

includes the minimum/maximum working volumes for each vessel, as well as the particular tasks associated with the solution preparation vessel and any process equipment necessary to complete solution preparation. The solution preparation tasks and equipment may be included in the total solution preparation time 1428 for use in equipment preparation and scheduling.

Next, step 1408 determines the water collection time for each preparation vessel. The water collection time is the amount of time necessary to fill the maximum working volume 1406 of the solution preparation vessel at the water collection rate 1404. Water collection rate 1404 is the rate at which the solution preparation vessel can be filled. Different solution preparation vessels have different water collection rates, depending on their specific water collection hardware. Step 1408 estimates the water collection time for each solution preparation vessel based on its maximum working volume 1410 and the water collection rate 1404. In the preferred embodiment, the volume of water to be collected is assumed to be the preparation vessel maximum working volume 1406. In alternative embodiments, the volume of water to be collected can be the actual volume of solution prepared in the solution preparation cycle. Examples of water collection rate 1404, maximum working volume 1406 and water collection time 1502 are illustrated in FIG. 15, columns 1404, 1406 and 1502, respectively.

Step 1414 defines the weigh and mix times associated with each solution preparation vessel. Weigh and mix time 1416 is the time required to weigh, mix and adjust the components of a solution. Preparation vessel identifiers 1402 are matched with the associated preparation vessel weigh and mix time 1416. The weigh and mix time 1416 associated with each solution preparation vessel in the biopharmaceutical process is thereby assigned to the associated solution preparation vessel identifier 1402. The default weigh and mix time variables can be manipulated by the process designer. Examples of weigh and mix time 1416 are illustrated in FIG 15, column 1416.

Next, step 1418 determines the time required to filter the solution in a preparation vessel. The time required to filter the solution in a preparation vessel

is the amount of time post-preparation filtering and transfer of the prepared solution out of the solution preparation vessel requires. Step 1418 calculates the time required to filter the solution in a preparation vessel based on preparation vessel identifier 1402, preparation vessel maximum working volume 1406, filtration flux rate 1424 and surface area of filtration media 1412. In the preferred embodiment, the volume of solution to be filtered is assumed to be the preparation vessel maximum working volume 1406. In alternative embodiments, the volume of solution to be filtered can be the actual volume of solution prepared in the solution preparation cycle. The surface area of the filtration media 1412 is the area of the filtration media used to filter the solution as it is transferred out of the solution preparation vessel. Filtration flux rate 1424 is the rate per unit area that the solution is can be filtered through the filtration media. Examples of filtration flux rate 1424 and surface area of filtration media 1412 are illustrated in FIG. 15, columns 1424 and 1412, respectively

Step 1426 calculates the adjusted filtration time. The adjusted filtration time is the filtration time as determined in step 1418 multiplied by the filtration delay factor 1430. Filtration delay factor 1430 is based on the additional filtration time typically required to manipulate solution storage vessels on a fill line. Step 1426 calculates the adjusted filtration time by multiplying the filtration time calculated in step 1418 by the filtration delay factor 1430. FIG. 15, column 1430 shows exemplary values for filtration delay factor 1430.

Step 1432 determines clean in place and steam in place durations associated with each solution preparation vessel. Clean in place duration 1422 and steam in place duration 1434 are the durations of the cleaning procedures necessary to prepare a solution preparation vessel for use in the next solution preparation cycle. Step 1432 matches preparation vessel identifiers 1402 with clean in place duration 1422 and steam in place duration 1434 to determine the clean in place duration 1422 and steam in place duration 1434 times associated with each of the solution preparation vessel used in the biopharmaceutical

production process. FIG. 15, columns 1422 and 1434 illustrate exemplary values for clean in place duration 1422 and steam in place duration 1434, respectively.

Step 1436 calculates total solution preparation time 1428 for each preparation vessel by summing the time values calculated in steps 1420, 1408, 1414, 1418, 1426 and 1432. Total solution preparation time 1428 represents the amount of time required to prepare the maximum working volume 1406 of solution in a particular solution preparation vessel. It should be noted, however, that one of ordinary skill could expand the calculation of total solution preparation time 1428 to include additional steps, factors or parameters other than those described herein. Such expansion would allow the present invention to calculate the total solution preparation time 1428 for a solution preparation vessel more accurately, or to include additional factors in the calculation. In addition, the calculation of total solution preparation time 1428 for a solution preparation vessel could also be adjusted to accommodate solution preparation working volumes which are less than the maximum solution preparation working volumes for a given solution prep vessel. Column 1428 of FIG 15 provides exemplary values for total solution preparation time 1428.

FIG. 15 shows an exemplary list of solution preparation parameters. Examples of such parameters are minimum working volume 1402, maximum working volume 1406, set up time 1410, water collection rate 1404, water collection time 1502, weigh and mix time 1416, square area of filter media 1412, volume per unit of filter area per hour 1424 and post-solution preparation and cleaning procedure duration 1422, 1434.

Minimum working volume 1402 and maximum working volume 1406 are the minimum and maximum volumes of solution a solution preparation vessel can prepare. Set up time 1410 is the amount of time necessary to prepare a solution preparation vessel for the solution preparation process. Water collection time 1404 is the time necessary to fill the solution preparation vessel with the maximum working volume 1406 of water. Weigh and mix time 1416 is the time necessary to weigh and mix the ingredients of a solution in a particular solution preparation

vessel. Square area of filter medium 1412 is the area of the filter associated with a particular solution preparation vessel. Volume per unit of filter area per hour 1424 is the flux rate per unit of filter area associated with a particular solution preparation vessel. Post solution preparation and cleaning procedure duration 1422 and 1434 are the times associated with preparing the solution preparation vessel after the preparation of a batch of solution.

FIG. 16 further illustrates step 1304, assigning the solutions required by the biopharmaceutical production process to particular solution preparation vessels. In order to schedule solution preparation cycles, each solution must be assigned to a solution preparation vessel. Step 1304 begins with step 1602. Step 1602 sets the preparation cycles per batch for a solution to be prepared. Preparation cycles per batch 1608 are the number of times a solution is prepared in a solution preparation vessel to support one product batch cycle. For example, if one-hundred and fifty liters of solution 101 is required to make a batch of product in a biopharmaceutical production process and the solution is to be prepared in a fifty liter solution preparation vessel, solution 101 may be prepared in three preparation cycles per batch of fifty liters each, yielding a 150 liter batch of solution 101. Alternatively, solution 101 may be prepared in four preparation cycles per batch of thirty-seven and one-half liters each in a solution preparation vessel of at least thirty-seven and one-half liters. In the preferred embodiment, preparation cycles per batch 1608 of solution is initially set by the designer. Preparation cycles per batch 1608 will affect values throughout the solution preparation scheduling module and the solution preparation procedure as a whole. The number of preparation cycles per batch 1608 for each solution will dictate the size of a solution preparation vessel and the time required to prepare a batch of solution.

Step 1606 determines the number of days per solution preparation cycle 1610 for each of the solutions involved in the biopharmaceutical production process. The number of days per solution preparation cycle 1610 is determined from preparation cycles per batch 1608 and days per batch cycle 1604. The batch

cycle time is the amount of time required to produce one batch of product. Days per batch cycle 1604 is the number of days between successive batches of product. The number of days per preparation cycle 1610 is the number of days between the beginnings of each solution preparation. Dividing the number of days per batch cycle by the preparation cycles per batch 1608 yields the number of days per preparation cycle 1610. For example, if one-hundred and fifty (150) liters of solution per batch of product is to be prepared in a solution preparation vessel with a working volume of fifty liters, the preparation cycles per batch 1608 is three. If one batch of biopharmaceutical product is produced every 6 days, the days per batch cycle 1604 is six. Given that there are three preparation cycles per batch for a particular solution, and there are six days per batch cycle, the number of days per preparation cycle 1610 is determined to be two. That is, there are two days between the beginnings of each fifty liter preparation cycle of solution.

Decision step 1612 checks the shelf life of the solution against the number of days per preparation cycle 1610. In the preparation of solutions, it is possible that the number of days per preparation cycle 1610 may exceed the shelf life of the solution. In such a situation, it is possible to have "stale" solution available for use in the biopharmaceutical production process because it has been held too long. If decision step 1612 determines that number of days per preparation cycle 1610 is greater than the shelf life, step 1304 continues at step 1602 where the number of preparation cycles per batch 1608 is adjusted (preferably increased). Adjusting the preparation cycles per batch 1608 of the solution will allow the solution preparation process designer to decrease the number of days per preparation cycle 1610 as determined in step 1606. If decision step 1612 determines that the number of days per preparation cycle 1610 is less than the shelf life of the instant solution, step 1304 continues at step 1616.

Step 1616 calculates the liters per preparation cycle of solution 1620 for each solution. Liters per preparation cycle of solution 1620 is calculated by dividing the total liters per batch for each solution 1618 by the number of preparation cycles per batch 1608 as determined in step 1602. Total liters per

batch for each solution 1618 is the quantity of each solution type needed to produce a batch of product in the biopharmaceutical production process and is stored in the material balance table.

Step 1624 determines the solution preparation vessel type for the preparation of each solution. Step 1624 assigns each solution to a solution preparation vessel in step 1624, generating preparation vessel to solution assignment list 1626. Step 1624 assigns each solution to a solution preparation vessel based on the number of liters per preparation cycle of solution 1620 and preparation vessel identifier and associated volume list 1402. Solution preparation vessels are chosen from preparation vessel identifier and associated volume list 1402 in order to place liters per preparation cycle of solution 1620 within the minimum working volume 1402 and the maximum working volume 1406 range of a solution preparation vessel. Preparation vessel to solution assignment list 1626 is a list of solutions to be prepared in the biopharmaceutical production process, and their associated solution preparation vessel.

Fig. 17 illustrates exemplary values of data for the present invention. Column 1618 illustrates exemplary values for the total liters per batch for each solution 1618. Column 1608 illustrates exemplary values for number of preparation cycles per batch 1608. In the instant example, all of the solutions as shown in column 1608 are prepared in one preparation cycle per batch. Column 1604 illustrates exemplary values for days per batch cycle 1604. Column 1610 illustrates exemplary values of number of days per preparation cycle 1610 as determined in step 1606. In the instant example, since the number of preparation cycles per batch 1608 of solution is equal to one for all of the solutions in the solution production process, the number of days per preparation cycle 1610 equals the number of days per batch cycle 1604. Column 1614 illustrates exemplary values of shelf life of solution 1614. Column 1706 illustrates exemplary values for the outcome of decision step 1612 where number of days per preparation cycle 1610 is compared to shelf life of solution 1614. Column 1618 of FIG. 17 illustrates exemplary values for total number of liters per batch for each solution



1618. Since the number of preparation cycles per batch 1608 for each of the solutions is one in the instant example, the number of liters per preparation cycle of solution 1620 is equal to total liters per batch for each solution 1618.

Columns 1708-1728 of FIGS. 17 and 18 illustrate an exemplary solution to solution preparation vessel assignment list 1626. The tank identifiers run along the top of column 1708-1728 and the solution identifiers run along the vertical axis on the far left hand side of the tables in FIGS. 17 and 18. In FIG. 18, exemplary solution preparation vessel identifiers are placed in the columns horizontally opposed from the solution identifiers indicating that the preparation vessel is assigned to that solution.

FIG. 18 illustrates exemplary preparation vessel to solution assignment list 1626. Columns 1626 illustrates preparation vessel to solution assignments. Column 1722 illustrates solution preparation vessel #108 is associated with solutions S-0107, S-0108, S-0112, S-0115, S-0117, and S-0120. Similarly, column 1724 illustrates solution preparation vessel #109 is associated with solutions S-0116, S-0118, and S-0119. Column 1726 illustrates solution preparation vessel #110 is associated with solutions S-0106 and S-0114. Column 1728 illustrates solution preparation vessel #111 is associated with solutions S-0101 and S-0113.

FIG. 20 further illustrates step 1306, determining the calculated start date for preparation of each solution 2010 and the next preparation date for each solution 2022. The next preparation date 2022 is based on the calculated start date 2010 and the number of days per solution preparation cycle 1610. Step 1306 begins at step 2004, determining the calculated start date for the preparation of each solution ("calculated start date") 2010. Calculated start date 2010 is the date by which the preparation of a solution should begin in order to prepare the solution in time for use in the biopharmaceutical production process. The calculated start date 2010 is determined by calculating back from the earliest date a solution is needed 2006 in the biopharmaceutical production process and the "lead time" needed to prepare and test a batch of solution before use. In the

preferred embodiment, the back calculated values are the total solution preparation time for a solution preparation vessel 1428, the number of back days to allow for a failed lot of solution 2002 and the number of hold days for solution quality assurance and quality control (QA/QC) testing 2008. If a batch of solution fails QA/QC testing, the solution will have to be prepared again, and this lead time is expressed as the number of back days to allow for a failed lot of solution 2002. The earliest date a solution is required 2006 comes directly from the process time line via the material balance table. The material balance is a list of solution formulation reagents and calculation sets, each of which is associated with a unit operation. The material balance table includes the volumes of all the process streams in the block flow diagram 704 and their constituent solution components according to the formulation of the solution. The material balance table also identifies the time that a solution is required in the manufacturing process according to the task scheduling data in the process time line 906.

After the calculated start date for solution preparation 2010 is determined, it is assigned to the associated solution and prep vessel solution assignment list 1626 resulting in a calculated start date 2010 for the preparation of each solution and its associated solution preparation vessel.

Step 2018 calculates the next solution preparation date for each solution after the calculated start date 2010 has been determined for each solution by selecting the greater of days for batch or days for preparation. Step 2018 calculates the next solution preparation date for each solution by. The next solution date is calculated in step 2018 by adding the number of days per preparation cycle 1610 to the calculated start date for preparation of each solution assigned to a preparation vessel 2010.

FIG. 24 further illustrates step 1308, determining the earliest solution preparation start date for each solution preparation vessel in a process cycle. Step 1308 begins by determining and assigning the calculated solution preparation start dates 2010 to each solution preparation vessel in step 2402. Solution preparation vessel ("prep vessel") to solution assignment list 1626 and calculated solution

preparation start date for all solutions 2010 are cross-referenced to generate calculated and assigned solution prep start dates to prep vessels 2404. Step 2406 generates the earliest solution preparation start date for each solution preparation vessel ("earliest start date") 2408. Calculated and assigned solution prep start dates to prep vessels 2404 is processed in step 2406 to determine the earliest solution preparation start date associated with each preparation vessel. Step 2406 results the earliest preparation start dates assigned to each preparation vessel 2408. This list provides the solution preparation vessels necessary for the biopharmaceutical production process, as well as the earliest date each solution preparation vessel is needed for preparation of solution in the process cycle.

FIG. 25 further illustrates step 1310, determining the latest solution preparation start date for each solution preparation vessel. Step 1310 begins by determining and assigning the next solution preparation dates to each solution preparation vessel at step 2502. A next solution preparation date is the date that a solution preparation vessel will be needed for the preparation of solution next after the earliest start date 2408. The solution preparation vessel to solution assignment list 1626 and next solution preparation date for each solution 2022, as determined in step 2018, are matched to generate a list of next solution preparation dates to each preparation vessel at step 2502. Next, step 2504 determines the latest next solution preparation start date associated with each preparation vessel 2506. The latest next solution preparation start dates are those dates associated with preparation vessels which signify the last preparation of solution procedure to occur in a particular solution preparation vessel during a process cycle.

FIG. 26 further illustrates step 1311, calculating solution preparation vessel utilization time for each solution preparation vessel 2604. Solution preparation vessel utilization time 2604 for each preparation vessel is that time during which the vessel is occupied with the preparation of solution(s) for a particular manufacturing cycle. Solution preparation vessel utilization time 2604 is the duration between the earliest preparation start date 2408 and the end of

latest next solution preparation cycle. The end of latest next solution preparation cycle is calculated by adding the total solution preparation time for a solution preparation vessel 1428 to the latest next solution preparation start date for each solution preparation vessel 2506, which results in the date when the solution preparation vessel has completed preparing solution in a process cycle. Solution preparation vessel utilization time for each solution preparation vessel 2604 is determined by comparing the earliest solution preparation start date 2408 with the sum of the latest next solution preparation start date 2506 and the total solution preparation time for each solution preparation vessel 1428.

FIG. 27 further illustrates step 1312, calculating the cumulative solution preparation time for each solution preparation vessel 2708. Cumulative solution preparation time for each solution preparation vessel 2708 is the amount of time that each preparation vessel is actually occupied with the preparation of solution. Essentially, cumulative solution preparation time is the product of the total solution preparation time for a solution preparation vessel 1428 and the number of solution preparation cycles that the solution preparation vessel is used for in the manufacturing cycle. For example, if the total solution preparation time for a solution preparation vessel is six hours per cycle, and the solution preparation vessel is used in the preparation of six cycles of solution, the cumulative solution preparation time 2708 is thirty-six hours.

Step 1312 begins by assigning a solution preparation total time for each solution preparation vessel to each preparation vessel at step 2702. Total solution preparation time for each preparation vessel 1428 from step 1302 is matched to preparation vessel to solution assignment list 1626. The lists of preparation vessels, the solutions associated therewith and their total solution preparation times are input into step 2704. Step 2704 determines the cumulative solution preparation time for each solution by multiplying the total solution preparation time 1428 for the solution preparation vessel by a solution's respective number of preparation cycles per batch 1608. Step 2704 results in the amount of time each solution preparation vessel is occupied with the preparation each particular

solution. Step 2706 determines the cumulative solution preparation time for each solution preparation vessel 2708 by summing the amount of time each solution preparation vessel is actually occupied with the preparation of solution. Steps 2704 and 2706 result in the list of cumulative solution preparation times for each preparation vessel 2708.

FIG. 28 further illustrates step 1314, determining the percentage utilization of each solution preparation vessel. The percentage utilization of a solution preparation vessel is the ratio of the cumulative total solution preparation time for each solution preparation vessel 2708 to the total time that a solution preparation vessel is available for solution preparation 2802 expressed as a percentage. Determining the percentage utilization of each solution preparation vessel 2808 allows the process designer to tailor the preparation cycles per batch 1602 of each solution to maximize the utilization of the solution preparation equipment, thereby minimizing cost and maximizing efficiency. Step 1314 begins by calculating the total number of hours a solution preparation vessel is available at step 2802. The total number of hours a preparation vessel is available is the product of the solution preparation vessel utilization time 2604, as determined in step 2602, and the hours per solution preparation shift 2804. The hours per solution preparation shift 2804 is provided from in the original process design parameters for the biopharmaceutical production process. For example, if the process is designed as a two shift process, the plant would normally run sixteen hours a day, and the number of hours per solution prep shift 2804 would be sixteen.

Step 2802 multiplies the solution preparation vessel utilization time 2604 by the hours per solution preparation shift per day 2804. Step 2802 results in the number of raw hours that a solution preparation vessel is available to the biopharmaceutical production process. For example, if the solution preparation vessel utilization time 2604 is six days, and the biopharmaceutical production process is run one shift a day (eight hours), the number of hours the solution preparation vessel is available for use in the biopharmaceutical production process is forty-eight. Forty-eight is the maximum number of hours that the solution

preparation vessel is available for use. If such a solution preparation vessel is actually occupied with the preparation of solution for twenty-four hours, the percentage utilization of the solution preparation vessel during its period of availability 2808 would be fifty percent.

Step 2806 calculates the percentage utilization of each solution preparation vessel. The percentage utilization 2808 is determined by comparing the total number hours a solution preparation vessel is available as calculated in step 2802 with the cumulative total solution preparation time for each solution preparation vessel 2708. By dividing cumulative total solution preparation time for each solution preparation vessel 2708 by the total number of hours a preparation vessel is available as calculated in step 2802, percentage utilization of each preparation vessel during its period of availability 2808 is calculated, as explained in the example above.

FIG. 29 further illustrates step 1316, generating the initial shift schedule 2910. The initial shift schedule 2910 is a table of dates scheduling the preparation of solutions for use in the biopharmaceutical production process. Initial shift schedules 2910 are generated for each of the solution preparation vessels. An initial shift schedule for a solution preparation vessel contains the solutions to be prepared and their associated preparation dates, as well as the days per prep cycle. FIG. 31 is an example of an initial shift schedule. Step 1316 begins with step 2902, generating a time-line starting from the earliest start prep date of all the solutions required by the biopharmaceutical production process at step 2902. In the preferred embodiment, the time-line is incremented one day at a time, out to a date predetermined by the system designer. In alternative embodiments, the time-line and shift schedule are incremented or delimited in whichever time intervals are most convenient.

Step 2904 determines and matches solution preparation dates for each solution 2404 with the dates in the shift schedule time-line from step 2902. Matched solution preparation dates to solution preparation vessels 2404 are entered into the shift schedule time-lines for each of the solution preparation

vessels. Starting from the calculated start date 2404, step 2904 enters successive preparation start dates for each solution associated with a preparation vessel based on the number of days per preparation cycle 1610. For example, if a particular solution assigned to solution preparation vessel has two days per preparation cycle, the solution is scheduled for preparation in its solution preparation vessel every two days after its calculated start date 2010. Step 2904 results in a list of solutions and associated preparation dates for each solution preparation vessel 2906.

Step 2908 enters the total number of solution preparation hours for each solution into each initial shift schedule time-line. The result is the number of preparation hours each day associated with every solution preparation in the initial shift schedule. Step 2908 matches solution preparation times for each solution preparation vessel 1428 with the dates assigned in each of the shift schedule time-lines to generate the initial shift schedule 2910. The total number of hours each solution preparation vessel is occupied with the preparation of solution each day can then be determined by adding the number of solution preparation hours associated with each day on an initial shift schedule time-line 2910. In the preferred embodiment, the number of hours of solution preparation per day per solution preparation vessel is essentially the product of the number of solution preparation cycles and the total solution preparation time for the solution preparation vessel 1428. For example, if a solution preparation vessel has a total solution preparation time for the solution preparation vessel 1428 of five hours, and is scheduled for four solution preparation cycles, the solution preparation vessel is scheduled for twenty hours of solution preparation that day. Step 2910 results in the initial shift schedule with solution identifiers and their solution preparation times assigned to their respective shifts 2910.

FIG. 31 is an example of an initial shift schedule for solution preparation vessel 101. Exemplary solution identifiers are shown in column 3102. Column 3102 illustrates exemplary solution identifiers for the solutions used in the biopharmaceutical production process. Solution identifiers 3102 with date entries

in corresponding An exemplary value for hours per solution prep shift is given in box 2804. Exemplary values for number of days per preparation cycle is given in column 1610. Exemplary values of solution prep dates of each solution is given in column 2906.

FIG. 30 further illustrates step 1318, back scheduling solution preparation in the initial shift schedule. Solution preparation is initially scheduled in steps 1302-1316 without considering the possibility of scheduling conflict. Back scheduling solution preparation is done in order to avoid conflicts in the solution preparation process. Scheduling conflicts result from scheduling more solution preparation cycles for a solution preparation vessel than can be accommodated in the amount of time available. For example, a scheduling conflict will occur if a particular solution preparation vessel is scheduled for twenty hours of solution preparation on one sixteen hour day. The present invention back schedules those solution preparation cycles that do not fit into their scheduled shift or day. For example, if a solution preparation vessel is scheduled for three solution preparation cycles of three hours each, the solution preparation vessel is scheduled for nine hours of preparation activity. If the production facility runs on an eight hour day, not all of the solutions can be prepared as scheduled. The present invention back schedules one of the solution preparation cycles, leaving six hours of solution preparation to be completed in one day. The back scheduled solution preparation cycle is rescheduled to the first previous available shift so that the solution is prepared in time for use in the biopharmaceutical production process as scheduled in the process time line. After step 1318 is completed, the solution preparation time line is in proper form for use as a solution preparation and scheduling and management tool.

Step 1318 begins at step 3002, successively summing the solution preparation times for each of the days or shifts in the initial shift schedule 2910 the solution preparation times are summed in order to determine the total solution preparation time for each solution preparation vessel on each shift. For the purpose of summing the solution preparation times, a shift is the number of hours



in one biopharmaceutical production process day (e.g., eight hours for a single shift plant, sixteen hours for a double shift plant, etc.). Step 2002 results in a list for each solution preparation vessel of summed solution preparation times for each shift 3004. Summed solution preparation times 3004 are compared with the available shift hours/day 2804 in step 3006. If the sum of the scheduled solution preparation times 3004 exceeds the number of shift hours available 2804, solutions are marked as “back scheduled” and are rescheduled for the first previously available shift. From the previous example, one of the three hour solution preparation cycles is to be rescheduled for the first previously available shift, leaving six hours of solution preparation in the eight hour shift. If the originally scheduled day for the nine hours of solution preparation was Wednesday, the three hour solution preparation would be back scheduled to Tuesday. After a solution that doesn't fit into the current day has been back scheduled, it is removed from the current day schedule.

If step 3006 determines that the number of shift hours 2804 available exceeds the sum of the scheduled solution preparation times 3004, step 3010 determines if any solution is scheduled for preparation on the current shift. If step 3010 determines that a solution is scheduled for preparation in the current shift, step 3012 leaves the solution scheduled for preparation in the shift schedule.

If step 3010 determines that no solutions are assigned to the solution preparation vessel for the shift that is being evaluated, step 1318 continues to step 3014. Step 3014 determines if any solutions have been back scheduled to the current shift for preparation for a later shift. If no solution preparation cycles have been back scheduled to the current shift, the process continues to step 3002 where the next shift is analyzed for back scheduling. If step 3014 determines that solution preparation cycles have been back scheduled, the process continues at step 3016. Step 3016 checks the original scheduling date on the back scheduled solution preparation cycle to determine if the back scheduled date is earlier than the original scheduling date minus the periodicity of the back scheduled solution. For example, if the solution has been successively back scheduled for four days

(i.e., the preparation cycle of the solution had to be scheduled back four days in order to fit into a shift), and its periodicity was two days, the back scheduled prep would be potentially interfering the previously scheduled prep of the same solution thereby indicating a shift schedule capacity error.

If step 3016 determines that the solution is back scheduled beyond its periodicity, an alarm is raised indicating that a system capacity issue exists at step 3020. If step 3016 determines that the back scheduled solution preparation cycle not earlier than its orbitally scheduled date minus its periodicity, the solution preparation cycle is scheduled for the current shift at step 3018.

FIG. 32 further illustrates step 1320, generating solution preparation schedule 3210. Solution preparation schedule 3210 schedules each task associated with solution preparation for the biopharmaceutical process based on the back-scheduled shift schedule 3202 and the solution preparation procedure 3212. Solution preparation schedules 3210 are generated for each solution preparation vessel that has an assigned solution. Back-scheduled initial shift schedule 3202, as generated in Step 1318, contains the solution preparation vessel to solution preparation assignment for each of the shifts in the initial shift schedule 2910. Step 1320 is performed for each of the shifts in the initial shift schedule 2910, thereby scheduling all of the solution preparation tasks for each solution preparation vessel on each shift.

Step 1320 begins at Step 3206, determining the number of solution preparation that are scheduled for the current shift in the back-scheduled initial shift schedule 3202. If no solutions are scheduled for preparation, step 1320 continues to step 3204 which moves to the next shift in the back-scheduled initial shift schedule 3202. If there are solution preparations scheduled for the current shift, step 1320 continues to step 3208. Step 3208 generates the solution preparation schedule 3210 from the solution preparation procedure data 3212 for each solution preparation scheduled in the shift. For example, if two solutions are scheduled to be prepared in solution preparation vessel 101, each task in each solution preparation procedure is scheduled out in solution preparation schedule

3210. An exemplary solution preparation procedure 3212 is illustrated in FIG. 14 (steps 1420, 1408, 1414, 1418, 1426, 1432, and 1436).

FIG. 15 illustrates exemplary solution preparation procedure data, as described above, used to generate solution preparation schedule 3210. Step 3208 schedules out each task for each solution preparation assigned to the current shift. After step 3208, and if there are additional shifts in the back-scheduled initial shift schedule 3202, step 1320 continues at step 3204 proceeding to the next shift in back-scheduled initial shift schedule 3202. Step 1320 repeats to schedule all of the solution preparations in the back-scheduled initial shift schedule. Step 1320 results in, therefore, solution preparation schedule 3210 which is a time line, by shift, for each solution preparation task for each solution preparation assigned to a solution preparation vessel.

### **3.0 Equipment Preparation Scheduling Module**

The object of the equipment preparation module is to simulate, schedule and model equipment preparation and loading in the biopharmaceutical production process. Equipment used in the biopharmaceutical production becomes soiled and must be cleaned, wrapped and sterilized in order to be used again. The process of cleaning, wrapping and sterilizing is known as equipment preparation. A piece of equipment that has been used in the biopharmaceutical production process and requires preparation before it can be used again is called a soiled process component. Equipment preparation is performed in order to sustain the biopharmaceutical production process.

Current methods for the design equipment preparation procedures typically fall short of accurately defining the relatively complex procedures that are executed in an equipment prep area. As a result the equipment and work areas associated with equipment prep are usually inefficiently designed. Since the cleaning and sterilizing (prep) equipment associated with equipment prep activities are capital and utility intensive, an improved method for accurately modeling and

optimizing these areas of a biopharmaceutical production facility is needed. The preferred embodiment provides a computer simulation method for the design and scheduling of equipment prep operations which is more accurate and efficient than conventional design methods.

FIG. 33 is a flowchart illustrating an overview of the process for scheduling and simulating equipment preparation in a biopharmaceutical production process. Step 3302 generates a preparation equipment protocol table. A preparation equipment protocol is a protocol for the operation of a piece of preparation equipment. Preparation equipment protocols usually include a plurality of equipment preparation tasks. A preparation task is a step in the equipment preparation process. For example, in a glassware dryer, a task may be loading the dryer, preheating the dryer, drying the glassware, unloading the dryer, etc. A preparation equipment protocol table is a set of standard preparation equipment protocols to clean soiled process components. Preparation equipment protocols are usually developed through experimentation and quality assurance testing. The preparation equipment protocols that prepare the soiled process components for reuse most effectively and to the required levels of cleanliness become the preparation equipment protocols.

Preparation equipment protocols are associated with specific pieces of preparation equipment. Examples of preparation equipment are bench sinks, wash stations, glassware washers, glassware dryers, carboy washers, carboy dryers, autoclaves, steam sterilizers, etc. Furthermore, there may be multiple preparation equipment protocols per piece of preparation equipment. For example, there may be four preparation protocols associated with each type of bench sink, each having different combinations of bench sink cleaning tasks and durations. Although the preferred embodiment describes a finite set of preparation equipment, soiled process components and preparation equipment protocols, one of ordinary skill could easily expand the process described herein to any preparation equipment or soiled process components.

Step 3304 generates an equipment preparation procedure table. An equipment preparation procedure is a standard procedure comprising a plurality of preparation equipment protocols by which a soiled process component is cleaned and sterilized for reuse in the biopharmaceutical production process. For example, an equipment preparation procedure for a carboy may include the preparation equipment protocols of bench sink rinsing, bench sink cleaning, carboy washing, carboy drying, wrapping and sterilization in an autoclave. Different types of soiled process components require different combinations of preparation equipment protocols in order to be readied for reuse in the biopharmaceutical production process, thereby defining different equipment preparation procedures. As with preparation equipment protocols, equipment preparation procedures are determined through experimentation, quality assurance and quality control. Each type of equipment used in the biopharmaceutical production process has an associated equipment preparation procedure.

An equipment preparation procedure table is a list of preparation equipment protocols and their associated information that define an equipment preparation procedure for each of the soiled process component types. In a preferred embodiment, there are equipment preparation categories for each piece of soiled process components. Instead of an equipment preparation procedure associated with each type of soiled process component, there is an equipment preparation procedure associated with each equipment preparation category. Preparation equipment protocols associated with each of the different equipment preparation categories are placed together in a table format to provide the preparation procedures for each piece of soiled process components assigned to an equipment preparation category.

Step 3306 generates the equipment dimension table. Equipment dimensions are the length, height and depth of a piece of process equipment requiring cleaning and sterilization (e.g., beaker, flask, carboy, stainless steel fittings, etc.). The equipment dimension table defines the dimensions of all process equipment potentially requiring cleaning after use in the biopharmaceutical

production process. The equipment dimension table is determined directly from the list of equipment used in the biopharmaceutical production process. The equipment dimension list provides a means for determining the volume of the equipment to be cleaned in the biopharmaceutical production process, thereby allowing the calculation of the capacity of the preparation equipment

Step 3308 generates a master list of equipment that may require preparation. Each unit operation in the biopharmaceutical production process is associated with preparation equipment. Step 3308 generates a master list of equipment associated with the biopharmaceutical production process and solution preparation process. In the preferred embodiment, the preparation equipment associated with each unit operation for both the biopharmaceutical production process and solution preparation process is defined when the unit operations for these activities are defined. As described above, the process equipment associated with unit operations of a biopharmaceutical production process are incorporated into a production process time line. Likewise the activities associated with each step of solution preparation is identified in step 1302 and incorporated into total solution preparation time for the solution preparation vessels 1428.

Step 3310 generates the equipment preparation load table. The equipment preparation load table includes data describing when particular soiled process components from the equipment dimension table are available for preparation. For example, some information comes from the finish times for the tasks in process time line 906 that define when the soiled process components from the biopharmaceutical production process will be available for cleaning. Step 3310 generates the equipment preparation load table by comparing the process time line schedule with the equipment preparation master list.

Step 3312 generates the equipment preparation load summary table. The equipment preparation load summary table is the sum of all equipment preparation load tables from each of the biopharmaceutical production processes active in the biopharmaceutical facility. For example, a facility may be producing multiple biopharmaceutical products in multiple processes. In such a case, the preparation

equipment handles equipment preparation for multiple biopharmaceutical production processes. Likewise, a facility may have multiple solution preparation suites. In such a case, the preparation equipment handles equipment preparation for multiple solution prep suites. Step 3312 generates the equipment preparation load summary table for the sum of all biopharmaceutical production processes by combining the equipment preparation load tables for all of the biopharmaceutical production processes.

Step 3314 estimates the preparation equipment capacity. The capacity of the preparation equipment is determined in order to provide sufficient capacity to handle the load of soiled process components in the biopharmaceutical facility. Preparation capacity is the flow rate of soiled process components that the preparation equipment can accommodate. Preparation capacity is estimated based on the flow rate of equipment from the preparation load summary table. The rate at which soiled process components are generated in the biopharmaceutical production facility is a good estimate of the capacity of the preparation equipment.

Step 3316 determines the equipment preparation time line. The equipment preparation time line includes scheduling each soiled process component through each piece of preparation equipment in each of the equipment preparation procedures. Functional specifications for the preparation equipment and the utility load requirements for the preparation equipment can be generated from the equipment preparation time line. Functional specifications describe a piece of equipment with particularity. For example, functional specifications for a pump include pump type, flow rate, maximum and minimum input and output pressures, input and output fitting sizes, electrical requirement, temperature range and type and frequency of required maintenance.

FIG. 34 further illustrates step 3302, generating the preparation equipment protocol table. Step 3302 begins with step 3404, generating the preparation equipment protocol identifiers 3408. Preparation equipment protocol identifiers 3408 are keys or codes which identify each preparation equipment protocol. Preparation equipment protocol identifiers 3408 allow each preparation equipment

protocol to be identified in the equipment preparation module and are used to generate the preparation equipment protocol table. Step 3404 assigns unique preparation equipment identifiers 3408 to each of the preparation equipment protocols 3402. Preparation equipment protocol table 3402 also includes the task and duration information associated with each preparation equipment protocol. Next, step 3406 generates preparation equipment protocol table 3410. Preparation equipment protocol table 3410 is generated by assigning preparation equipment protocol identifiers 3408 to each preparation equipment protocol in preparation equipment protocol table 3402.

FIGS. 36A-36H are exemplary preparation equipment protocol tables 3410. Column 3408 in FIGS. 36A-36H illustrate exemplary preparation equipment protocol identifiers 3408. Preparation equipment protocol table 3410 contains information describing each preparation protocol. Preparation equipment protocol identifiers BS-1 through BS-5 identify individual bench sink preparation protocols. For example, FIG. 36A illustrates protocol task durations for the bench sink preparation equipment. Protocol task duration is the amount of time associated with a task in a preparation equipment protocol. For example, protocol BS-1 in FIG. 36A has a loading task duration of 5 minutes. Bench sink protocol BS-1, therefore, includes the step of loading the bench sink, which requires 5 minutes. Protocol task durations of prewash rinse with non-potable hot water (NPHW), prewash rinse with non-potable cold water (NPCW), detergent wash with reagent, post wash rinse with NPHW and NPCW, final rinse and hold dry are illustrated in FIG. 36A. Columns 3602 and 3604 are examples of protocol parameters. Protocol parameters are data elements that describe particular facets of a preparation equipment protocol. In the example of FIG. 36A, protocol parameters detergent wash reagent and grams of reagent per cubic foot are used to describe the detergent in the bench sink wash process.

FIG. 36B illustrates an exemplary preparation equipment protocol table for a wash station. Column 3408 of FIG. 36B illustrates exemplary preparation equipment protocol identifiers 3408 for a wash station. FIG. 36C illustrates an



exemplary preparation equipment protocol table for a glassware washer. Column 3408 in FIG. 36C illustrates exemplary preparation equipment protocol identifiers 3408 for a glassware washer. FIG. 36D illustrates an exemplary preparation equipment protocol table 3410 for a glassware dryer. Column 3408 in FIG. 36D illustrates exemplary preparation equipment protocol identifiers 3408 for a glassware dryer. FIG. 36D illustrates exemplary task durations for tasks associated with the glassware dryer protocols. Some examples of task durations are loading 3618, heat up 3620, drying 3624, cooling 3626 and unloading 3628, as shown by their respective columns. Column 3622 illustrates the drying temperature protocol parameter. FIG. 36E illustrates an exemplary preparation equipment protocol table 3410 for a carboy washer. FIG. 36F illustrates an exemplary preparation equipment protocol table 3410 for a carboy dryer.

FIG. 36G illustrates an exemplary preparation equipment protocol table for a steam sterilizer. Due to the multiple protocol parameters and task durations associated with steam sterilizer preparation equipment protocols, the preparation equipment protocol table of FIG. 36G is two-dimensional. Row 3608 illustrates exemplary preparation equipment protocol identifiers 3408 for the steam sterilizer. The steam sterilizer preparation equipment protocol table 3410 includes multiple protocol tasks 1-33 as illustrated in column 3606. Each of the tasks in the steam sterilizer protocol has associated protocol parameters and protocol durations as illustrated in columns 3608, 3610, 3612, 3614 and 3616. Row 32 in column 3606 of FIG. 36G illustrates exemplary values for the total time in minutes required for each of the different steam sterilizer protocols (protocol identifiers SS-1, SS-2 and SS-3). FIG. 36H illustrates an exemplary preparation equipment protocol table 3410 for a dry heat stabilizer.

FIG. 35 further illustrates step 3304 generating equipment preparation procedure table 3512. Equipment preparation procedure table 3512 includes data associated with each equipment preparation procedure, including the sequence of preparation equipment protocols and their individual durations as well as their cumulative duration over the entire procedure. Step 3304 begins at step 3506,

generating equipment preparation procedure identifiers 3510. Equipment preparation procedure identifiers are tags or codes which identify equipment preparation procedures. FIGS. 37A and 37B illustrate an exemplary equipment preparation procedure table 3512. Row 3702 illustrates exemplary equipment preparation procedure identifiers 3510. EPC-1, EPC-2, EPC-3, EPC-4, EPC-5, EPC-6 and EPC-7 are examples of codes which identify equipment preparation procedures.

Step 3508 generates equipment preparation procedure table 3512. Step 3508 generates equipment preparation procedure table 3512 from preparation equipment protocol tables 3502, equipment preparation procedures 3504 and equipment preparation procedure identifiers 3510. Equipment preparation procedures 3504 provides the list of preparation equipment protocols that identify a particular equipment preparation procedure and equipment assignment. FIG. 37A, for example, shows equipment preparation procedure EPC-1 includes (as shown in column EPC-1) preparation equipment protocols BS-1, BS-3, GD-1, and SS-1 in FIG. 37B. Equipment preparation procedures 3504 also include the equipment assignments for each of the equipment preparation procedures. Equipment assignments define the soiled process components associated with, or prepared by, each equipment preparation procedure. For example, a particular equipment preparation procedure may only be used to clean carboys. Step 3508 compares the preparation equipment protocols in the equipment preparation procedures 3504 with the preparation equipment protocol tables 3502. The protocol durations and protocol parameters provide the information in equipment preparation procedures table 3512. Equipment preparation procedure identifiers 3510 are assigned to each individual equipment preparation procedure in equipment preparation procedure table 3512.

FIGS. 37A and 37B illustrate exemplary equipment preparation procedure tables 3512. Row 3702 illustrates exemplary equipment preparation procedure identifiers EPC-1, EPC-2, EPC-3, EPC-4, EPC-5, EPC-6, and EPC-7. Equipment preparation procedure identifiers 3510 identify equipment preparation procedures

for different categories of equipment. Exemplary equipment preparation procedure identifier EPC-5 includes the preparation equipment protocols of wash station (WS-1), carboy washer (CW-1), carboy dryer (CD-1), and steam sterilization autoclave 1 (SS-2). Associated with each of the preparation equipment protocols are task durations. Column 3704 illustrates task durations for equipment preparation procedure EPC-5. The task durations for each of the preparation equipment protocols are totaled to yield the equipment preparation procedure duration for EPC-5. Cumulative totals for the equipment preparation procedure duration are given in column 3706, rows 8, 15, 24, 31, 38, 45, 52, 66, 75 and 82. The cumulative durations are the sum of all the previous preparation equipment protocol durations in the equipment preparation procedure.

FIG. 38 further illustrates step 3306, generating equipment dimension table 3816. Step 3306 begins at step 3806, generating the master equipment dimension list 3808. Step 3806 uses the list of equipment requiring preparation 3802 and the equipment dimensions list 3804 to generate master equipment list 3806 which defines the dimensions of all process equipment that may cleaned by the equipment preparation procedure. List of equipment requiring preparation 3802 is a complete list of all the equipment used in the biopharmaceutical production process. List of equipment requiring preparation 3802 may be generated from the unit operations that define the process time line 906 or solution preparation schedule. Alternatively, list of equipment requiring preparation 3802 may be provided by the system designer as the equipment used in the biopharmaceutical production process by design. List 3802 identifies those pieces of equipment that will need to be prepared in order to complete the biopharmaceutical production process. Equipment dimensions list 3804 is a master list of equipment dimensions for all of the equipment available for use in the biopharmaceutical production process. Often, equipment dimensions list 3804 will be provided by the vender or manufacturer of the process equipment. List of equipment requiring preparation 3802 is compared to the equipment dimensions list 3804 in order to assign the

equipment dimensions to the equipment used in the biopharmaceutical production process, resulting in master equipment dimension list 3808.

Next, step 3812 generates the equipment dimension table with segregated equipment preparation procedure identifiers. Step 3812 segregates the equipment dimension list into equipment preparation procedures as defined in the equipment preparation procedures and equipment assignment list 3504. The master equipment dimension list 3808 is segregated based on the equipment preparation procedure identifiers 3510 in order to generate equipment dimension table 3816 according to equipment preparation procedure identifiers. The resultant equipment dimension table 3816 includes a list of specific process equipment and their associated equipment preparation procedure identifiers. Each particular equipment preparation procedure (e.g., EPC-1, EPC-2, EPC-3, etc.) is assigned to particular equipment types. Equipment dimension table 3816 also includes the dimensions of equipment to be prepared.

FIG. 39 illustrates an exemplary equipment dimension table 3816. Row 3902 illustrates exemplary equipment preparation procedure identifiers 3510. Rows 3904 identify the dimensions of each particular type of equipment involved in the equipment preparation process. Rows 3904 illustrates exemplary values for the dimensions of soiled process components to be cleaned in the equipment preparation procedure. Row 1 of rows 3904 illustrates exemplary values for the right-to-left dimension (R/L) in inches. Row 2 of rows 3904 illustrates exemplary values for the front-to-back dimension (F/B) in inches. Row 3 of rows 3904 illustrates exemplary values for top-to-bottom dimensions (T/B) in inches. Row 5 of rows 3904 illustrates exemplary values for volume in cubic inches (CI). Row 6 of rows 3904 illustrates exemplary values for volume in cubic feet (CF). CI and CF are computed directly from the rectilinear dimensional values in rows 1-3 of rows 3904.

Column 3906 illustrates exemplary dimensional values for siphon tube equipment in equipment preparation procedure EPC-1. Column 3908 illustrates exemplary dimensional values for instruments including pressure indicators (PI),

optical density probe and pH probe. Column 3910 illustrates exemplary dimensional values for fittings including tees, elbows, crosses, reducers, hose barbs and clamps. Column 3912 illustrates exemplary dimensional values for small and medium plasticware. Column 3914 illustrates exemplary dimensional values for silicone and butyl rubber stoppers. Column 3916 illustrates exemplary dimensional values for small and large flexible tubing. Column 3918 illustrates exemplary dimensional values for small and medium glassware. Column 3920 illustrates exemplary dimensional values for one, twenty and forty-five liter polypropylene carboys. Column 3922 illustrates exemplary dimensional values for ten, twenty and forty-five liter borosilicate glass carboys.

FIG. 40 further illustrates step 3308, generating equipment preparation master list 4004. Equipment preparation master list 4004 includes the process equipment that may be soiled by unit operation tasks and the solution preparation procedure tasks in the biopharmaceutical production process. As described above, each task in unit operation master list 508 has associated process equipment. The process equipment associated with each unit operation task is added to the equipment preparation master list 4004 in step 4002. Step 4002 uses unit operation master list 508 to generate a master list of equipment that may require preparation after use in the biopharmaceutical production process. Each piece of equipment has an associated dimension as defined in equipment dimension table 3816. Step 4002 compares unit operation master list 508 with equipment dimension table 3816 to assign the equipment dimensions to the equipment in unit operation master list 508 when generating equipment preparation master list 4004. Step 4002 compares solution preparation task list 4006 with equipment dimension table 3816 to assign the equipment dimensions to the solution preparation task list 4006 when generating equipment preparation master list 4004. After step 4002, equipment preparation master list 4004 contains the list of process equipment used in the biopharmaceutical production process that may become soiled process components requiring cleaning by the equipment preparation procedures.

FIG. 41 further illustrates step 3310, generating equipment preparation load table 4104. Equipment preparation load table 4104 includes data indicating when soiled process components from the equipment preparation master list 4004 will be available from the biopharmaceutical production process. Step 4102 generates equipment preparation load table 4104 by combining solution preparation schedule 3210 and process time line 906 with equipment preparation master list 4004. Cumulative flow of equipment out of the biopharmaceutical production process as represented by solution preparation schedule 3210 and process time line 906 is compared with equipment preparation master list 4004 in order to provide the equipment dimensional information in equipment preparation load table 4104. Equipment preparation load table 4104 includes soiled process components, the schedule for when the soiled process components are available for equipment preparation procedures, the dimensional information associated with each soiled process component and which task in the biopharmaceutical production process or solution preparation process generated the soiled process components. Equipment preparation load table 4104 represents the volumetric flow rate of equipment out of the biopharmaceutical production process that needs to be prepared for later use in order to sustain continuous biopharmaceutical production.

FIGS. 42A-42E illustrate an exemplary equipment preparation load table 4104. Column 4202 illustrates exemplary task titles. Task titles 4202 may originate from solution preparation procedure tasks or the titles of tasks in unit operations. Column 4204 illustrates exemplary task end times. The values in columns 4204 represent the date and time various soiled process components will be available for cleaning and preparation in equipment preparation procedures. Columns 4206-4216 of FIGS. 42A and 42B illustrate exemplary values for soiled process components available for preparation in equipment preparation procedures. In each of the columns, each of the soiled process components contains the number and cubic footage with which it is associated. FIGS. 42C-42D illustrate additional tasks in the biopharmaceutical production process.

As before, columns 4218-4228 of FIGS. 42C-42D illustrate exemplary values for soiled process components available for preparation in equipment preparation procedures.

FIG. 43 further illustrates step 3312, generating equipment preparation load summary table 4304. Equipment preparation load table 4104 defines when soiled process components from the equipment preparation master list 4004 will be available from all biopharmaceutical production processes active in the biopharmaceutical facility. Because single equipment preparation facilities may be shared across multiple biopharmaceutical production processes, the equipment load tables 4104 are combined to create equipment preparation load summary table 4304. Equipment preparation load summary table 4304 allows the scheduling and simulation of equipment preparation procedures for the entire biopharmaceutical production facility

FIG. 44 further illustrates step 3314, determining the capacities of the preparation equipment 4416. Step 3314 begins with step 4404, generating an initial equipment preparation schedule 4408. An initial equipment preparation schedule 4408 is generated for each equipment preparation procedure (EPC-1, EPC-2, EPC-3, etc.). As stated above, each equipment preparation procedure is associated with specific soiled process components. The initial equipment preparation schedule 4408 begins prior to the earliest date that soiled process components are available, as provided by the equipment preparation load summary table 4304

The initial equipment preparation schedule 4408 is an initial schedule for the arrival of soiled process components at each piece of preparation equipment. Since the duration of each task in each of the equipment preparation procedures is known, the time at which soiled process components arrive at various preparation equipment is calculated directly by adding the duration of each task from the preparation equipment protocol table 3410 to the equipment preparation load summary table 4304. The time at which each soiled process component arrives at a particular step in a preparation equipment protocol is the sum of

previous equipment preparation procedure tasks and the time which the soiled process component became available, as indicated in the equipment preparation load summary table 4304. Scheduling the soiled process components that arrive at each piece of preparation equipment allows the peak loading on the preparation equipment to be determined. The peak loading of the preparation equipment can then be used to determine the size and capacity of the preparation equipment.

Step 4412 compares the peak cubic footage load, as determined in step 4410, with the cubic footage of the largest soiled process component from the equipment dimension table 3816. Step 4412 selects the larger of the peak cubic foot load and the cubic footage of the largest equipment item from the equipment dimension table.

Step 4414 uses the larger peak CF value as determined in step 4412 to generate the capacities for the preparation equipment 4416. Capacities for the preparation equipment 4416 will need to be high enough to handle the peak cubic footage of soiled process components that need to be prepared in the equipment preparation procedure. The capacities determined in step 4414 and stored in table 4416, therefore, are the maximum capacities for the preparation equipment. Once the necessary capacity for the preparation equipment has been determined, an equipment prep time line can be generated.

FIG 46 further illustrates step 3316, generating the equipment preparation time lines 4610. Equipment preparation time lines 4610 include scheduling information for each soiled process component through each piece of preparation equipment in equipment preparation procedures. Equipment preparation time line 4610 includes the schedule of operation for each piece of preparation equipment. Equipment preparation time lines 4610 also include scheduling information for each particular facet of preparation equipment operation including resource loads for labor, utilities, disposables, reusables, maintenance, calibration, etc. Together with the capacity data determined in step 4414, equipment preparation time line 4610 allows the determination of functional specifications for preparation equipment to which cost and other data can be matched.



Step 3316 begins with step 4606, generating the final equipment preparation shift schedules for each piece of preparation equipment. As stated above, after the preparation equipment capacities have been determined in step 3314, the maximum load capacities for the preparation equipment 4602 are known. Capacities for preparation equipment 4416 define the maximum load capacities for preparation equipment 4602. Minimum load capacity for preparation equipment 4604 is a value set by the biopharmaceutical production process designer in order to maximize efficiency or for the validation of equipment preparation procedure. For example, a biopharmaceutical production process designer may determine that sterilizer equipment should not be operated at less than fifty percent of its load capacity. The sterilizer equipment, therefore, would be operated only when sufficient volume of soiled process components have been accumulated. Step 4606 generates the final equipment preparation shift schedules for each piece of equipment based on the maximum load capacities for preparation equipment 4602, the minimum load capacities for preparation equipment 4604, and equipment preparation procedure table 3512. The final equipment preparation shift schedules include the load cycling through the preparation equipment dictated by the minimum load capacities 4604 and the maximum load capacities 4602. Maximum load capacities 4602 and minimum load capacities 4604 define when each particular protocol in the equipment preparation procedure table 3512 is executed. The final equipment preparation shift schedules contain accurate scheduling of the operation of each

Step 4608 generates the equipment preparation time lines 4610. The equipment preparation time lines 4608 differ from the final equipment preparation shift schedules, as determined in step 4606, by providing detailed scheduling of the tasks associated the prep equipment protocols in equipment prep procedure table 3512. Equipment preparation time lines 4610 are generated by comparing equipment preparation procedure table 3512 with the final equipment preparation shift schedules for each piece of preparation equipment. Equipment preparation

time lines 4610 contain the time data for specific tasks and operation of preparation equipment.

FIG. 47 illustrates the process of generating preparation equipment functional specifications 4706. Preparation equipment functional specifications list 4706 contains functional specifications and costs associated with each piece of preparation equipment used in the equipment preparation procedure. Maximum load capacities for preparation equipment 4602 is used with equipment preparation time lines 4610 to provide the necessary specifications for the preparation equipment in the preparation equipment procedure. Step 4704 compares the specifications of maximum load capacities 4602 and equipment preparation time lines 4610 to determine which preparation equipment units from master equipment and cost list 4702 are required for the equipment preparation procedures. Master equipment and cost list 4702 contains the functional specifications of all of the available preparation equipment and their associated costs. Preparation equipment is selected from master equipment and cost list 4702 based on functional specification matching with equipment preparation time lines 4610 and maximum load capacities for the preparation equipment 4602. The result of step 4704 is preparation equipment list with functional specifications and cost 4706, which is a subset of master equipment and cost list 4702. Preparation equipment list with functional specifications and costs 4706 provides a means to more accurately match required preparation equipment with detailed cost and other data such as loads for utilities maintenance, calibration, quality assurance and quality control testing, etc.

FIG. 48 illustrates a process of generating preparation equipment utility time line 4810. The preparation equipment utility time line 4810 provides the utility requirements for the equipment preparation process. The preparation equipment utility time line 4810 includes the utility requirements for each piece of preparation equipment and the associated date and time for the requirements. The preparation equipment utility time line 4810 allows the calculation of utility costs associated with each piece of preparation equipment and allows a

biopharmaceutical facilities designer to determine the necessary utility supply to the preparation equipment. The process of generating preparation equipment utility time line 4810 begins with step 4804, generating the preparation equipment utility table. The preparation equipment utility table includes a list of the preparation equipment functional specifications from preparation equipment list 4706 matched with the utility data for each piece of preparation equipment as given by preparation equipment utility data 4802. Preparation equipment utility data 4802 includes the requirements for each piece preparation equipment during each task in a preparation equipment protocol. Examples of utility data are electrical power requirements, potable and nonpotable hot and cold water requirements, waste water requirements, steam requirements, etc. Step 4804 generates preparation equipment utility table 4806 by matching the data from equipment preparation equipment list 4706 with preparation equipment utility data 4802 on a preparation equipment by preparation equipment basis.

Step 4808 generates preparation equipment utility time line 4810. Step 4808 matches the data in preparation equipment utility table 4806 with equipment preparation time line 4610 to generate preparation equipment utility time line 4810. Preparation equipment utility time line 4810 schedules out the utility requirements for each piece of preparation equipment on a for each task in the preparation equipment protocols. Each of the tasks in equipment preparation time line 4610 is matched to the data in preparation equipment utility table 4806. Based on equipment preparation time line 4610 and the utility requirements for each piece of preparation equipment as described in preparation equipment utility table 4806, the utility requirements for each of preparation equipment is scheduled out in preparation equipment utility time line 4810. The utility time line 4810 when combined with the utility time lines from other manufacturing operations such as biopharmaceutical production, solution preparation, etc. provides peak loading data for the accurate sizing of utilities. The detailed data of the equipment time lines allows for the identification and optimization of utility peak loads and cost through the analysis of well documented operations schedules

#### **4.0     *Equipment Maintenance Scheduling Module***

Equipment maintenance in a biopharmaceutical production facility is necessary to sustain the biopharmaceutical production process. The types and frequency of maintenance required is a function of the particular equipment used in the facility, as well as the frequency and nature of use. The equipment involved in the production process, solution preparation process, and equipment preparation all require regular maintenance during sustained operation. Often, maintenance frequency and cost are not considered in the design of a biopharmaceutical production facility. Maintenance costs, however, are a significant fraction of the cost of operating the biopharmaceutical facility and producing the biopharmaceutical product. Since maintenance is a significant cost of operating a biopharmaceutical production facility, a system and method for scheduling and modeling the maintenance of process equipment, solution preparation equipment and preparation equipment would allow the biopharmaceutical facility designer to predict and minimize the cost of maintenance. Additionally, scheduling and modeling maintenance of a biopharmaceutical production process would allow for more complete modeling of a biopharmaceutical production facility.

Modeling and scheduling biopharmaceutical production facility maintenance is based on the functional specifications and usage of the biopharmaceutical production process equipment. Each piece of equipment has associated maintenance parameters. For example, a particular pump may require a new drive belt, seals and lubrication after a predetermined number of hours of operation. Filtration media in filters must be changed after a predetermined number of hours of use. Given equipment functional specifications, equipment maintenance requirements and production schedules for biopharmaceutical production process equipment, equipment maintenance can be modeled and scheduled.

FIG. 49 illustrates the process of generating process equipment maintenance table 4906. Process equipment maintenance table 4906 includes maintenance procedures, maintenance duration (i.e., the amount of time required to perform the maintenance), reusables (i.e., those maintenance items that must be replaced periodically), disposables (i.e., those maintenance items that must be replaced after every use), the maintenance period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the maintenance tasks for the equipment.

Step 4904 generates process equipment maintenance tables 4906 from the process equipment list and functional specifications 4908 and process equipment maintenance data 4902. Process equipment list 4908 is generated from unit operation list 508. Unit operation list 508 includes the process equipment associated with each task in a unit operation. The process equipment list 4908, therefore, includes a list of process equipment from unit operation list 508. Process equipment list 4908 also includes functional specifications associated with each piece of process equipment in process equipment list 4908. Functional specifications describe a piece of equipment with particularity. For example, functional specifications for a pump include pump type, flow rate, maximum and minimum input and output pressures, input and output fitting sizes, electrical requirement, temperature range and type and frequency of required maintenance.

Functional specifications associated with each piece of process equipment are determined from the block flow diagram 704, process time line 906 and equipment data sheets. Equipment data sheets, usually vendor or manufacturer provided, are equipment specifications that provide the capacity and functional specifications for equipment available for use in the biopharmaceutical production processes. Each unit operation has associated process equipment. The functional specifications of the equipment, however, are rate- and time-dependent. Block flow diagram 704 defines the volume of solution and biopharmaceutical product handled by each unit operation. The process time line 906 defines the rate at which solutions and biopharmaceutical product are handled in each unit operation

The volume and rate information from the block flow diagram and process time line, therefore, define the operational parameters of the process equipment. The functional specifications of the process equipment are determined directly by matching the volume and rate parameters for the equipment with the volume and rate parameters in equipment data sheets. The functional specifications of the equipment from the equipment data sheet are then added to the process equipment list to form process equipment list with functional specifications 4908.

Step 4904 generates process equipment maintenance table 4906 from process equipment list with functional specifications 4908 and process equipment maintenance data 4902. Process equipment maintenance data 4902 includes functional specifications for each piece of process equipment and their associated maintenance information. Process equipment maintenance data 4902 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item. Some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each maintenance item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per cycle. Also included in process equipment maintenance data 4902 is the amount of labor associated with each maintenance item and the number of dollars per cycle for the labor.

Step 4904 matches process equipment list with functional specifications 4908 with process equipment maintenance data 4902, to generate process equipment maintenance table 4906. Process equipment list with functional specifications 4908 is matched with process equipment maintenance data 4902 based on a comparison of functional specifications in the process equipment list 4908 and the process equipment maintenance data 4902. Step 4904 copies the process equipment maintenance data 4902 for each piece of process equipment in the process equipment list 4908, thereby creating process equipment maintenance table 4906.

FIGS. 64A-64AB illustrate an exemplary process equipment maintenance table 4906. Column 6402 illustrates exemplary unit operations and their associated process equipment, as determined from process equipment list 4908. FIGS. 64A-64E illustrate the process equipment maintenance data for unit operations 1-6, as illustrated in column 6402.

Column 6404 of FIG. 64A illustrates exemplary maintenance data values for the filter maintenance items. Included in column 6404 are item number, quantity, cycle life of the filter materials, unit cost of the filter materials, dollars per cycle of the filter material, the labor of hours required to service the filter media, and the dollars per cycle for the labor. Item number identifies the stock number or part number of the item used in the maintenance procedure. Cycle life of the materials identifies the useful life the maintenance item. Quantity identifies the quantity of the maintenance item used in the maintenance procedure. Unit cost is the per unit cost of the maintenance item. Dollars per cycle is the quotient of the cost of the maintenance items and the cycle life of the maintenance items.

Column 6406 illustrates exemplary maintenance data for gasket maintenance items. Column 6408 of FIGS. 64A and 64B illustrates exemplary maintenance data for bearing maintenance items. Column 6410 of FIG. 64B illustrates exemplary maintenance data for seal maintenance items. Column 6412 of FIGS. 64B and 64D illustrate exemplary maintenance data for belt maintenance items. Column 6416 of FIG. 64C illustrates exemplary maintenance data for crank shaft maintenance items. Column 6418 of FIGS. 64C and 64D illustrates exemplary maintenance data for lubricant maintenance items. Column 6420 of FIG. 64D illustrates exemplary maintenance data for thermal media maintenance items. FIGS. 64E-64AB illustrate the same maintenance items as described in column 6404-6420, as associated with unit operations 7-22.

FIG 50 illustrates the process of generating the process equipment maintenance time line 5004. Process equipment maintenance time line 5004 is a schedule maintenance items or procedures for process equipment in the biopharmaceutical production process. Step 5002 generates process equipment

5 maintenance time line 5004 by applying the equipment scheduling data from the  
process equipment time line 906 data to the process equipment maintenance table  
4906. Step 5002 calculates the accumulated usage time for each piece of  
equipment and schedules maintenance on the equipment at the times specified by  
10 the process equipment maintenance table 4906. Process equipment maintenance  
time line 5004 includes process equipment maintenance data from process  
maintenance data 4906 and the specific time and date when each piece of process  
equipment should be serviced. Step 5002, therefore, determines the number of  
unit operations or process cycles required to attain the cycle life rating on the  
15 maintenance item in order to trigger the maintenance processes.

FIG. 51 illustrates the process of generating solution preparation  
equipment maintenance table 5106. Solution preparation equipment maintenance  
table 5106 includes maintenance procedures, maintenance duration (i.e., the  
amount of time required to perform the maintenance), reusables (i.e., those  
20 maintenance items that must be replaced periodically), disposables (i.e., those  
maintenance items that must be replaced after every use), the maintenance period  
(i.e., the amount of use before the equipment must be serviced), and the number  
of hours required to complete the maintenance tasks for the equipment.

Step 5104 generates solution preparation equipment maintenance table  
25 5106 from the solution preparation equipment list and functional specifications  
5108 and solution preparation equipment maintenance data 5102. Solution  
preparation equipment list 5108 is generated from preparation vessel identifier and  
associated volume list 1402. Preparation vessel identifier and associated volume  
list 1402 includes the solution preparation equipment associated with each solution  
30 preparation vessel. The solution preparation equipment list 5108, therefore,  
includes a list of solution preparation equipment from preparation vessel identifier  
and associated volume list 1402. Solution preparation equipment list 5108 also  
includes functional specifications associated with each piece of solution  
preparation equipment in solution preparation equipment list 4809. The functional  
specifications for each solution preparation vessel and its associated solution



preparation equipment are included in preparation vessel identifier and associated volume list 1402 when it is defined.

Step 5104 generates solution preparation equipment maintenance table 5106 from solution preparation equipment list with functional specifications 5108 and solution preparation equipment maintenance data 5102. Solution preparation equipment maintenance data 5102 includes functional specifications for each piece of solution preparation equipment and their associated maintenance information. Solution preparation equipment maintenance data 5102 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item. Some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each maintenance item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per cycle. Also included in solution preparation equipment maintenance data 5102 are the amount of labor associated with each maintenance item and the number of dollars per cycle for the labor.

Step 5104 matches solution preparation equipment list with functional specifications 5108 with solution preparation equipment maintenance data 5102, to generate solution preparation equipment maintenance table 5106. Solution preparation equipment list with functional specifications 5108 is matched with solution preparation equipment maintenance data 5102 based on a comparison of functional specifications in the solution preparation equipment list 5108 and the solution preparation equipment maintenance data 5102. Step 5104 copies the solution preparation equipment maintenance data 5102 for each piece of solution preparation equipment in the solution preparation equipment list 5108, thereby creating solution preparation equipment maintenance table 5106.

FIG. 52 illustrates the process of generating the solution preparation equipment maintenance time line 5204. Solution preparation equipment maintenance time line 5204 is a schedule maintenance items or procedures for solution preparation equipment in the biopharmaceutical production process. Step

5202 generates process equipment maintenance time line 5204 by applying the equipment scheduling data from the solution preparation equipment time line 3210 data to the solution preparation equipment maintenance table 5106. Step 5202 calculates the accumulated usage time for each piece of equipment and schedules maintenance on the equipment at the times specified by the solution preparation equipment maintenance table 5106. Solution preparation equipment maintenance time line 5204 includes solution preparation equipment maintenance data from process maintenance data 5106 and the specific time and date when each piece of solution preparation equipment should be serviced. Step 5202, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the maintenance item in order to trigger the maintenance processes.

FIG 53 illustrates the process of generating preparation equipment maintenance table 5306. Preparation equipment maintenance table 5306 includes maintenance procedures, maintenance duration (i.e., the amount of time required to perform the maintenance), reusables (i.e., those maintenance items that must be replaced periodically), disposables (i.e., those maintenance items that must be replaced after every use), the maintenance period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the maintenance tasks for the equipment.

Step 5304 generates preparation equipment maintenance table 5306 from preparation equipment list with functional specifications 4706 and preparation equipment maintenance data 5302. Preparation equipment list 4706 also includes functional specifications associated with each piece of preparation equipment as determined in step 3314. Preparation equipment maintenance data 5302 includes functional specifications for each piece of preparation equipment and their associated maintenance information. Preparation equipment maintenance data 5302 includes replaceables, reusables, labor, cycle life and the cost of the associated maintenance item.

Step 5304 matches preparation equipment list with functional specifications 4706 with preparation equipment maintenance data 5302, to generate preparation equipment maintenance table 5306. Preparation equipment list with functional specifications 4706 is matched with preparation equipment maintenance data 5302 based on a comparison of functional specifications in the preparation equipment list 4706 and the preparation equipment maintenance data 5302. Step 5304 copies the preparation equipment maintenance data 5302 for each piece of preparation equipment in the preparation equipment list 4706, thereby creating preparation equipment maintenance table 5306.

FIG. 54 illustrates the process of generating the preparation equipment maintenance time line 5404. Preparation equipment maintenance time line 5404 is a schedule maintenance items or procedures for preparation equipment in the biopharmaceutical production process. Step 5402 generates process equipment maintenance time line 5404 by applying the equipment scheduling data from the preparation equipment time line 4610 data to the preparation equipment maintenance table 5306. Step 5402 calculates the accumulated usage time for each piece of equipment and schedules maintenance on the equipment at the times specified by the preparation equipment maintenance table 5306. Preparation equipment maintenance time line 5404 includes preparation equipment maintenance data from process maintenance data 5306 and the specific time and date when each piece of preparation equipment should be serviced. Step 5402, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the maintenance item in order to trigger the maintenance processes.

## **5.0 Equipment Calibration Module**

Equipment calibration in a biopharmaceutical production facility is necessary to sustain the biopharmaceutical production process. Equipment calibration is essential to the accurate measurement and control of all key

manufacturing operations. Instruments such as pressure indicators, temperature indicators, flow meters, load cells etc. are at the core of most manufacturing systems. The reliability of these instruments and the processes they serve is dependent on punctual and consistent calibration programs. The types and frequency of calibration required is a function of the particular equipment used in the facility, as well as the frequency and nature of use. The equipment involved in the production process, solution preparation process and equipment preparation all require regular calibration during sustained operation. Often, calibration frequency and cost are not considered in the design of a biopharmaceutical production facility. Calibration costs and scheduling, however, are a significant fraction of the cost of operating the biopharmaceutical facility and producing the biopharmaceutical product. Since calibration is a significant cost of operating a biopharmaceutical production facility, a system and method for scheduling and modeling the calibration of process equipment, solution preparation equipment and preparation equipment would allow the biopharmaceutical facility designer to predict and minimize the cost of equipment calibration. Additionally, scheduling and modeling equipment calibration of a biopharmaceutical production process would allow for more reliable calibration programs to insure the adequate and consistent performance of all manufacturing systems. .

Modeling and scheduling biopharmaceutical production equipment calibration is based on the functional specifications and usage of the biopharmaceutical production process equipment. Each piece of equipment has associated calibration points. These calibration points typically include pressure indicators and transmitters, temperature indicators and transmitters, level sensors, flow meters, etc. All of these calibration points are required for the reliable operation of these process systems. Given equipment functional specifications, equipment calibration requirements and production schedules for biopharmaceutical production process equipment, equipment calibration can be modeled and scheduled.

FIG. 55 illustrates the process of generating process equipment calibration table 5506. Process equipment calibration table 5506 includes calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), the calibration period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the calibration tasks for the equipment.

Step 5504 generates process equipment calibration table 5506 from process equipment list with functional specifications 4908 and process equipment calibration data 5502. Process equipment calibration data 5502 includes functional specifications for each piece of process equipment and their associated calibration information. Process equipment calibration data 5502 includes replaceables, reusables, labor, cycle life and the cost of the associated calibration item. As mentioned above, some examples of replaceables and reusables are: filters, gaskets, bearings, seals, belts, crank-shafts, lubricants and thermal media. Associated with each calibration item is the number and identifier for the item, the quantity, the cycle life (i.e., the amount of time or use before replacement), and the cost per cycle. Also included in process equipment calibration data 5502 are the amount of labor associated with each calibration item and the number of dollars per cycle for the labor.

Step 5504 matches process equipment list with functional specifications 4908 with process equipment calibration data 5502, to generate process equipment calibration table 5506. Process equipment list with functional specifications 4908 is matched with process equipment calibration data 5502 based on a comparison of functional specifications in the process equipment list 4908 and the process equipment calibration data 5502. Step 5504 copies the process equipment calibration data 5502 for each piece of process equipment in the process equipment list 4908, thereby creating process equipment calibration table 5506.

FIG. 56 illustrates the process of generating the process equipment calibration time line 5604. Process equipment calibration time line 5604 is a

schedule calibration items or procedures for process equipment in the biopharmaceutical production process. Step 5602 generates process equipment calibration time line 5604 by applying the equipment scheduling data from the process equipment time line 906 data to the process equipment calibration table 5566. Step 5602 calculates the accumulated usage time for each piece of equipment and schedules calibration on the equipment at the times specified by the process equipment calibration table 5566. Process equipment calibration time line 5604 includes process equipment calibration data from process calibration data 5566 and the specific time and date when each piece of process equipment should be serviced. Step 5602, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration item in order to trigger the calibration processes.

FIG. 57 illustrates the process of generating solution preparation equipment calibration table 5706. Solution preparation equipment calibration table 5706 includes calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), reusables (i.e., those calibration items that must be replaced periodically), disposables (i.e., those calibration items that must be replaced after every use), the calibration period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the calibration tasks for the equipment.

Step 5704 generates solution preparation equipment calibration table 5706 from the solution preparation equipment list and functional specifications 5108 and solution preparation equipment calibration data 5702. Solution preparation equipment list 5108 is generated from preparation vessel identifier and associated volume list 1402. Preparation vessel identifier and associated volume list 1402 includes the solution preparation equipment associated with each solution preparation vessel. The solution preparation equipment list 5108, therefore, includes a list of solution preparation equipment from preparation vessel identifier and associated volume list 1402. Solution preparation equipment list 5108 also includes functional specifications associated with each piece of solution

preparation equipment in solution preparation equipment list 4809. The functional specifications for each solution preparation vessel and its associated solution preparation equipment are included in preparation vessel identifier and associated volume list 1402 when it is defined.

Step 5704 generates solution preparation equipment calibration table 5706 from solution preparation equipment list with functional specifications 5108 and solution preparation equipment calibration data 5702. Solution preparation equipment calibration data 5702 includes functional specifications for each piece of solution preparation equipment and their associated calibration data.

Step 5704 matches solution preparation equipment list and functional specifications 5108 with solution preparation equipment calibration data 5702 to generate solution preparation equipment calibration table 5706. Solution preparation equipment list with functional specifications 5108 is matched with solution preparation equipment calibration data 5702 based on a comparison of functional specifications in the solution preparation equipment list 5108 and the solution preparation equipment calibration data 5702. Step 5704 copies the solution preparation equipment calibration data 5702 for each piece of solution preparation equipment in the solution preparation equipment list 5108, thereby creating solution preparation equipment calibration table 5706.

FIG. 58 illustrates the process of generating the solution preparation equipment calibration time line 5804. Solution preparation equipment calibration time line 5804 is a schedule of calibration items and procedures for solution preparation equipment in the biopharmaceutical production process. Step 5802 generates process equipment calibration time line 5804 by applying the equipment scheduling data from the solution preparation equipment time line 3210 data to the solution preparation equipment calibration table 5706. Step 5802 calculates the accumulated usage time for each piece of equipment and schedules re-calibration on the equipment at the times specified by the solution preparation equipment calibration table 5706. Solution preparation equipment calibration time line 5804 include solution preparation equipment calibration data from process calibration

data 5706 and the specific time and date when each piece of solution preparation equipment should be calibrated. Step 5802, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration of the equipment in order to trigger re-calibration of the equipment.

FIG. 59 illustrates the process of generating preparation equipment calibration table 5906. Preparation equipment calibration table 5906 include calibration procedures, calibration duration (i.e., the amount of time required to perform the calibration), the calibration period (i.e., the amount of use before the equipment must be serviced), and the number of hours required to complete the calibration tasks for the equipment.

Step 5904 generates preparation equipment calibration table 5906 from preparation equipment list with functional specifications 4706 and preparation equipment calibration data 5902. Preparation equipment list 4706 also include functional specifications associated with each piece of preparation equipment as determined in step 3314. Preparation equipment calibration data 5902 include functional specifications for each piece of preparation equipment and their associated calibration data. Preparation equipment calibration data 5902 includes labor, and cycle life of the associated with calibration.

Step 5904 matches preparation equipment list and functional specifications 4706 with preparation equipment calibration data 5902, to generate preparation equipment calibration table 5906. Preparation equipment list with functional specifications 4706 is matched with preparation equipment calibration data 5902 based on a comparison of functional specifications in the preparation equipment list 4706 and the preparation equipment calibration data 5902. Step 5904 copies the preparation equipment calibration data 5902 for each piece of preparation equipment in the preparation equipment list 4706, thereby creating preparation equipment calibration table 5906.

FIG. 60 illustrates the process of generating the preparation equipment calibration time line 6004. Preparation equipment calibration time line 6004 is a calibration schedule calibration for preparation equipment in the biopharmaceutical



production process. Step 6002 generates process equipment calibration time line 6004 by applying the equipment scheduling data from the preparation equipment time line 4610 data to the preparation equipment calibration table 5906. Step 6002 calculates the accumulated usage time for each piece of equipment and schedules calibration on the equipment at the times specified by the preparation equipment calibration table 5906. Preparation equipment calibration time line 6004 include preparation equipment calibration data from process calibration data 5906 and the specific time and date when each piece of preparation equipment should be calibrated. Step 6002, therefore, determines the number of unit operations or process cycles required to attain the cycle life rating on the calibration item in order to trigger the calibration processes.

## **6.0     *Quality Control Module***

Quality control in a biopharmaceutical production facility is necessary to ensure the safety and quality of the biopharmaceutical product. Quality control sampling and testing, at various points in the biopharmaceutical production process ensures contamination-free product during the process, solution preparation and equipment preparation. The type and frequency of quality control sampling and testing required in a biopharmaceutical production process is a function of the particular equipment used in the process, the frequency and nature of the equipment use and the particular step or task in which the equipment is engaged. Often, quality control testing, frequency and cost are not planned prior to the design of a biopharmaceutical production facility. Quality control, sampling and testing, however, play a significant role in scheduling the operation of a biopharmaceutical facility. Modeling and scheduling quality control sampling and testing in a biopharmaceutical production facility is based on the definitions of the basic steps in the biopharmaceutical production process. Quality control testing and sampling steps are specified for the production process, the solution preparation process and equipment preparation protocols.

FIG. 61 illustrates the process for generating a master quality control protocol table 6110. Quality control protocols are assays and testing procedures associated with quality control sampling and testing. Quality control protocols 6102 are defined by the biopharmaceutical facility designer, determined through testing and experimentation or specified by the vendor of the equipment in the biopharmaceutical facility. Quality control protocols 6102 include quality control protocol parameters. Quality control parameters are values that define the quality control assays. Examples of quality control parameters are the category and title of the assay, the setup time for the assay, the time required to draw each sample, the time required to clean up after taking the sample(s) and the disposal material necessary to dispose of the samples after testing.

Step 6104 generates quality control protocol identifiers 6108 for each of quality control protocols 6102. Quality control protocol identifiers 6108 are tags or codes that identify individual quality control protocols 6102. Step 6106 assigns quality control protocol identifiers 6108 to the quality control protocols 6102 resulting in master quality control protocol table 6110. Master quality control protocol table 6110 includes quality control protocols 6102 and a unique quality control identifier 6108 associated with each of quality control protocols 6102.

FIG. 21 illustrates an exemplary master quality control protocol table 6110. Column 2102 illustrates three exemplary categories of quality control protocols including environmental, analytical, and *in vitro* biological quality control protocols. Column 2104 illustrates exemplary quality control protocol identifiers 6108. Column 2106 illustrates exemplary values for quality control protocol parameters. More specifically, column 2106 illustrates quality control protocol parameters for the number of man-hours required to setup, draw each sample and cleanup the sampling operations associated with each quality control protocol. Setup and cleanup parameters define the amount of time necessary to setup prior to and cleanup after quality control protocol sampling. The per sample quality control protocol parameter defines the amount of time required to draw each sample. For example, 10 samples of temperature (quality control protocol

identifier E-1) would require 0.5 man-hours to set up, 1.0 man-hours to sample (0.1 hours/sample  $\times$  10 samples) and 0.5 man-hours to clean up.

FIG 62 illustrates the process of generating master quality control sample table 6208. Master quality control sample table 6208 includes all of the tasks and quality control sampling protocols associated with the production of a biopharmaceutical product. Each task or step in the process time line, the solution preparation schedule or the preparation equipment time line that has an associated quality control protocol 6102 is included in master unit operation list 6206. Each task or step in master unit operation list 6206 also includes a quality control protocol. The quality control protocol parameters of master quality control protocol table 6110 is used to generate master quality control sample list in step 6202. The master quality control sample list 6202 lists all the codes of the quality control protocols from the master QC protocol table 6110. Step 6204 uses the master quality control sample list to assign sampling assays to each step in master unit operation list 6206 according to which quality control protocol is assigned to each step in master unit operation list 6206. The result of step 6204 is a master QC sample table 6208 which includes all of the steps in the biopharmaceutical production process, solution preparation and equipment preparation as well as their associated quality control protocol and sample list.

FIG. 63 illustrates the process for generating the process equipment quality control time line 6304. Quality control process equipment time line 6304 is a table of all the unit operations associated with process equipment time line 906 as well as the schedule of quality control assays and samples associated with each. Step 6302 generates the process equipment quality control time line 6304. Step 6302 matches the process steps of process equipment 906 with master unit operation list 6206 to determine which assays need to be assigned to the tasks in process equipment time line 906. Step 6302 assigns the quality control samples to be taken in each of the associated tasks from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 6304.

FIGS 45A-45I illustrate an exemplary process equipment quality control time line 6304. Fig. 45A illustrates unit operations 1A-6A in column 4502. Scheduling for each of the tasks in unit operations 1A-6A is illustrated in columns 4504. Columns 4506 of FIGS. 45A-45B illustrate the quality control assays from master quality control protocol table 6110. Although columns 4506 are empty, if quality control samples were scheduled for unit operations 1A-6A in column 4502, columns 4506 would contain the number of samples to be taken at the scheduled time, as defined in master quality control sample table 6208. FIGS. 45C-45I illustrate the balance of the tasks and unit operations for the process equipment quality control time line 6304.

FIG. 22 illustrates the process for generating the solution preparation equipment quality control time line 2204. Quality control solution preparation equipment time line 2204 is a table of all the tasks associated with solution preparation schedule 3210, as well as the schedule of quality control assays and samples associated with each task. Step 2202 generates the solution preparation equipment quality control time line 2204. Step 2202 matches the solution preparation tasks of solution preparation schedule 3210 with master unit operation list 6206 to determine which assays need to be assigned to the tasks in solution preparation schedule 3210. Step 2202 assigns the quality control samples to be taken in each of the associated tasks with from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 2204.

FIG. 23 illustrates the process for generating preparation equipment quality control time line 2304. Quality control preparation equipment time line 2304 is a table of all the tasks associated with preparation equipment time line 4610, as well as the schedule of quality control assays and samples associated with each task in the preparation equipment protocols. Step 2302 generates the preparation equipment quality control time line 2304. Step 2302 matches the equipment preparation tasks of preparation equipment time line 4610 with master unit operation list 6206 to determine which assays need to be assigned to the tasks

in preparation equipment time line 4610. Step 2302 assigns the quality control samples to be taken in each of the associated tasks from master quality control sample table 6208 to each of the tasks in process equipment time line 906, resulting in process equipment quality control time line 2304.

## 5            **7.0    Environment**

10            The present invention may be implemented using hardware, software or a combination thereof and may be implemented in a computer system or other processing system. In fact, in one embodiment, the invention is directed toward a computer system capable of carrying out the functionality described herein. An example computer system 1901 is shown in FIG. 19. The computer system 1901 includes one or more processors, such as processor 1904. The processor 1904 is connected to a communication bus 1902. Various software embodiments are described in terms of this example computer system. After reading this description, it will become apparent to a person skilled in the relevant art how to  
15            implement the invention using other computer systems and/or computer architectures

20            Computer system 1902 also includes a main memory 1906, preferably random access memory (RAM), and can also include a secondary memory 1908. The secondary memory 1908 can include, for example, a hard disk drive 1910 and/or a removable storage drive 1912, representing a floppy disk drive, a magnetic tape drive, an optical disk drive, etc. The removable storage drive 1912 reads from and/or writes to a removable storage unit 1914 in a well known manner. Removable storage unit 1914, represents a floppy disk, magnetic tape, optical disk, etc. which is read by and written to by removable storage drive 1912.  
25            As will be appreciated, the removable storage unit 1914 includes a computer usable storage medium having stored therein computer software and/or data.

              In alternative embodiments, secondary memory 1908 may include other similar means for allowing computer programs or other instructions to be loaded

into computer system 1901. Such means can include, for example, a removable storage unit 1922 and an interface 1920. Examples of such can include a program cartridge and cartridge interface (such as that found in video game devices), a removable memory chip (such as an EPROM, or PROM) and associated socket, and other removable storage units 1922 and interfaces 1920 which allow software and data to be transferred from the removable storage unit 1922 to computer system 1901

Computer system 1901 can also include a communications interface 1924. Communications interface 1924 allows software and data to be transferred between computer system 1901 and external devices. Examples of communications interface 1924 can include a modem, a network interface (such as an Ethernet card), a communications port, a PCMCIA slot and card, etc. Software and data transferred via communications interface 1924 are in the form of signals which can be electronic, electromagnetic, optical or other signals capable of being received by communications interface 1924. These signals 1926 are provided to communications interface via a channel 1928. This channel 1928 carries signals 1926 and can be implemented using wire or cable, fiber optics, a phone line, a cellular phone link, an RF link and other communications channels.

In this document, the terms “computer program medium” and “computer usable medium” are used to generally refer to media such as removable storage device 1912, a hard disk installed in hard disk drive 1910, and signals 1926. These computer program products are means for providing software to computer system 1901.

Computer programs (also called computer control logic) are stored in main memory and/or secondary memory 1908. Computer programs can also be received via communications interface 1924. Such computer programs, when executed, enable the computer system 1901 to perform the features of the present invention as discussed herein. In particular, the computer programs, when executed, enable the processor 1904 to perform the features of the present

invention. Accordingly, such computer programs represent controllers of the computer system 1901.

In an embodiment where the invention is implemented using software, the software may be stored in a computer program product and loaded into computer system 1901 using removable storage drive 1912, hard drive 1910 or communications interface 1924. The control logic (software), when executed by the processor 1904, causes the processor 1904 to perform the functions of the invention as described herein.

In another embodiment, the invention is implemented primarily in hardware using, for example, hardware components such as application specific integrated circuits (ASICs). Implementation of the hardware state machine so as to perform the functions described herein will be apparent to persons skilled in the relevant art(s).

In yet another embodiment, the invention is implemented using a combination of both hardware and software.

## **8.0 Conclusion**

While the invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the relevant art that various changes in form and details may be made therein without departing from the spirit and scope of the invention.

***What Is Claimed Is:***

1           1       A method for scheduling and simulating solution preparation, said  
2       solution for use in a biopharmaceutical production process, comprising the steps  
3       of.

4           (1)     identifying at least one solution for preparation and its associated  
5       volume;

6           (2)     identifying a predetermined start date for preparation of said at  
7       least one solution and at least one successive start date for preparation of said at  
8       least one solution;

9           (3)     assigning said at least one solution to a to a preparation vessel; and

10          (4)     determining the duration of the solution preparation procedure  
11       based on said step of assigning said at least one solution to a preparation vessel.

1           2       The method of claim 1, wherein step (1) comprises the step of  
2       calculating the total volume of said at least one solution needed for one process  
3       cycle

1           3.       The method of claim 1, wherein the step (2) comprises the step of  
2       calculating the latest start date for preparation of said at least one solution  
3       necessary for the preparation of said at least one solution to be prepared in time  
4       for use in the biopharmaceutical process.



## **System and Method for Simulation, Modeling and Scheduling of Solution Preparation in Biopharmaceutical Batch Process Manufacturing Facilities**

### ***Abstract***

5           A method and system for simulating, modeling and scheduling solution  
preparation in the biopharmaceutical production process is described herein. The  
system and method includes the steps of identifying a solution for preparation and  
its associated volume. After the solution for preparation is identified, a  
predetermined start date and one successive start date for solution preparation for  
10 the solution are identified. After the solution, start and successive start dates are  
identified, the solution is assigned to a preparation vessel. After the solution has  
been assigned to a preparation vessel, the duration of the solution preparation  
procedure is determined and assigned to the solution preparation vessel.

a202-02.wpd

6/19/98

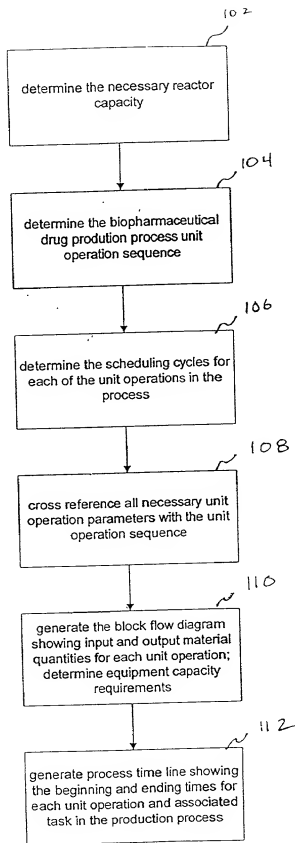


FIG. 1

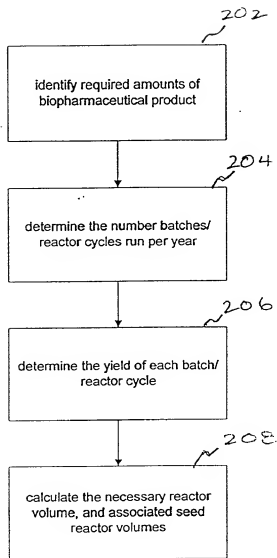


FIG. 2

## Unit Operations List

## Microbial Fermentation Process

UOP Seq. No.	Unit Operation Type	Cycles per										Recovery					
		UnOp		Batch				Process				Product		Total Protein			
		Offset (hrs)	UnOp (hrs)	UnOp Start	UnOp End	Offset (hrs)	UnOp Start	UnOp End	Offset (hrs)	UnOp Start	UnOp End	SWR	OAR	SWR	OAR		
1	Inoculum Prep	1	3	1	6	1	1	1									
2	Plank Growth	1	3	1	6	1	1	1									
3	Seed Fermentation	1	3	1	6	1	1	1									
4	Production Fermentation	1	3	1	6	1	1	1									
5	Heat Exchange	1	3	1	6	1	1	1									
6	Cont. Centrifugation/Whole Cell Harvest	1	3	1	6	1	1	1									
7	Resuspend Cell Paste	1	3	1	6	1	1	1									
8	Heat Exchange	1	3	6	10	1	6	10									
9	Centrifugation/High Pressure	1	3	8	10	1	8	10									
10	Heat Exchange	1	3	8	10	1	8	10									
11	Centrifugation/Surfactant	1	2	11	12	1	11	12									
12	Cont. Centrifugation/Precipitate Harvest	1	2	11	12	1	11	12									
13	Resuspend/Buffer	1	1	1	1	1	1	1									
14	Ultrafiltration/Concentration/Dilution	1	1	1	1	1	1	1									
15	Microfiltration/Tangential Flow	1	1	1	1	1	1	1									
16	Product Adsorption MPLC	1	1	1	1	1	1	1									
17	Product Adsorption MPLC	1	1	1	1	1	1	1									
18	Ultrafiltration/Flow Dialysis	1	1	1	1	1	1	1									
19	Product Adsorption MPLC	1	1	1	1	1	1	1									
20	Product Adsorption MPLC	1	1	1	1	1	1	1									
21	Ultrafiltration/Flow Dialysis	1	1	1	1	1	1	1									
22	Product Adsorption MPLC	1	1	1	1	1	1	1									
23	Microfiltration/Dead End	1	1	1	1	1	1	1									
302			306	308	312	314	316	318	320	322	324	326	328	330	332		
304																	

FIG. 3

## Mammalian Cell Culture Process

UOP Seq. No.	Unit Operation Type	Cycles per		Batch			Process			Recovery		
		UnOp		UnOp Start	UnOp End	Offset (hrs)	UnOp Start	UnOp End	Offset (hrs)	Product		
			Offset (hrs)							SWR	OAR	Total Protein SWR OAR
1	4 Initial Seeding	1										
2	5 Culture Vessel Split	1										
3	5 Culture Vessel Split	1										
4	5 Culture Vessel Split	1										
5	5 Culture Vessel Split	1										
6	5 Spinner Flask Split	1										
7	5 Spinner Flask Split	1										
8	13 Stirred Tank Reactor	1										
9	61 Harvest/Feed	7	24									
10	62 Harvest Pool	1										
11	34 MFT Tangential Flow	1										
12	36 UF Concentration	1										
13	39 PAC/MPLC	1										
14	39 PAC/MPLC	1										
15	39 PAC/MPLC	1										
16	39 PAC/MPLC	1										
17	37 UF/Flow Dialysis	1										
18	35 MF/Dead End	1										
19	99 End	1										
402		406		408	410	412	414	416	418	420	422	424

FIG. 4

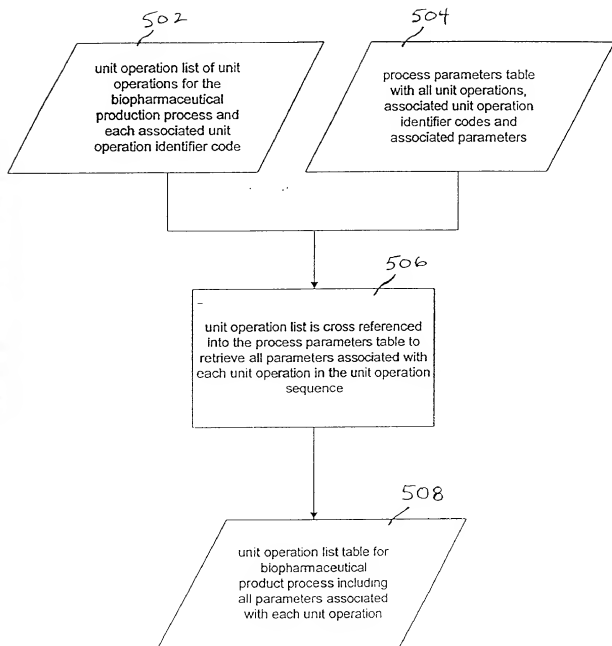


FIG. 5

unit operation id code	Unit operation type	Parameters	solution type	tasks	task duration
1	inoculum prep	# of flasks, volume of flasks, temperature, agitation, duration, final OD	S-101	setup, preincubation, incubation, clean up	3, 3, 23, .3 Hrs
2	flask growth	scale up ratio, media volume, temperature, agitation, duration, final OD	S-101	setup, preincubation, incubation, clean up	1, 1, 23, .3 Hrs
3	fermentation seed	scale up ratio, fermentor working volume, antifoam, base acid, grow temperature, agitation, sparge rate, back pressure, total duration	S-101, 102, 103, 104, 105	setup, preincubation, fermentation, harvest, CIP, SIP, clean up	1, 1, 21, .5, 1, 1, 3 Hrs
4	fermentation production	scale up ratio, fermentor working volume, antifoam A, antifoam B, base, acid, grow temperature, agitation, sparge rate, back pressure, total duration, final OK, dry cell mass, product concentration, CIP, SIP	S-101, 102, 103, 104, 105	setup preincubation, fermentation, CIP, SIP, cleanup	.
5	heat exchange	process Initial & final temp; utility Initial & final temp; process specific heat; design type, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP		setup, transfer, CIP, SIP, cleanup	.
6	batch centrifugation	system void volume, RCF, time, volume reduction, wash volume, clean, rinse	S-106	setup, centrifugation, wash, CIP, SIP, cleanup	.
7	resolubilization resuspension	reagent/product ratio, titration solution, resolubilization, agitation, solution name, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-107	setup, dilution, agitate, CIP, SIP, clean up	.
8	Cell Disruption High Press. Homogenization	product temperature, utility temperature, void volume, number of passes, pressure, flow rate, temperature increase, wash, rinse, step recovery of product, step recovery of T.P., temperature regulation, CIP	S-107	setup, lysis, CIP, SIP, clean up	.
9	Dilute with Surfactant	reagent product ratio, titration solution, dilution time, agitation, solution name, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-108	setup, dilution, agitate, CIP, SIP, clean up	.
10	batch centrifugation precipitate harvest	system void volume, RCF, time, volume reduction, wash volume, clean, rinse, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-108	setup, centrifugation, wash, CIP, SIP, clean up	.
11	resuspend with chaotrope	reagent/product ratio, titration solution, resolubilization, agitation, solution name, step recovery of product, step recovery of T.P., temperature regulation, CIP, SIP	S-109	setup, flush, prime, concentration, dilution, wash, flush, store, CIP, SIP, cleanup	.

Fig. 6

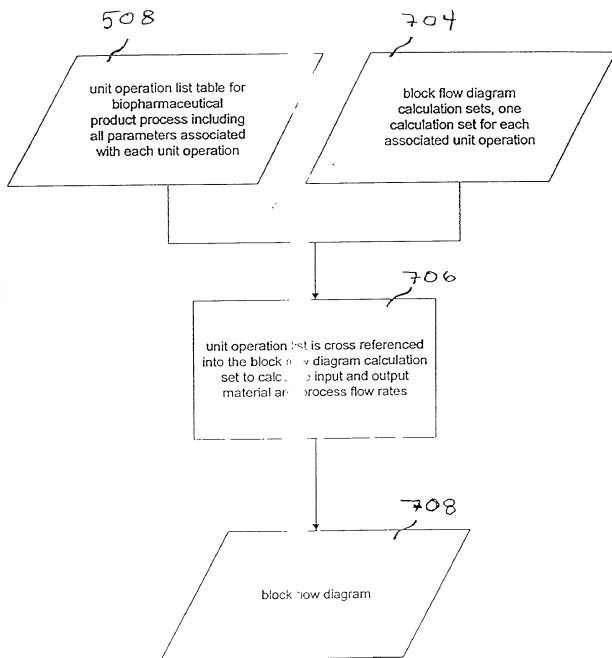


FIG. 7



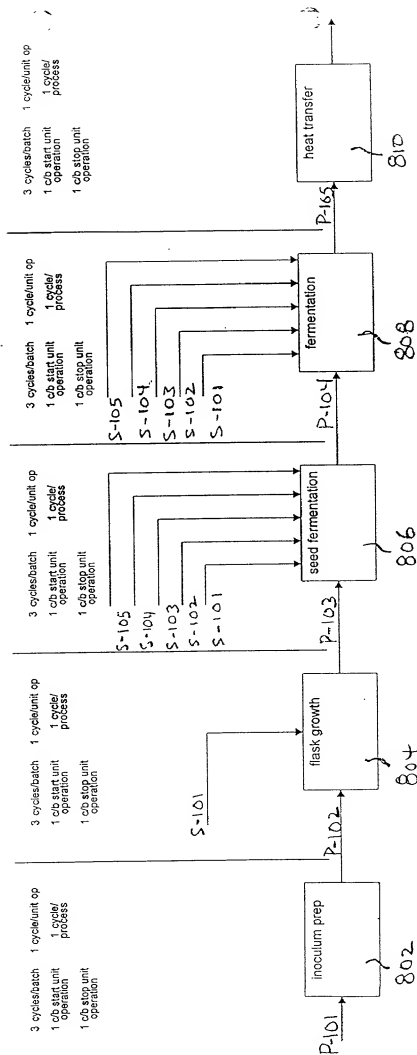


FIG. 8

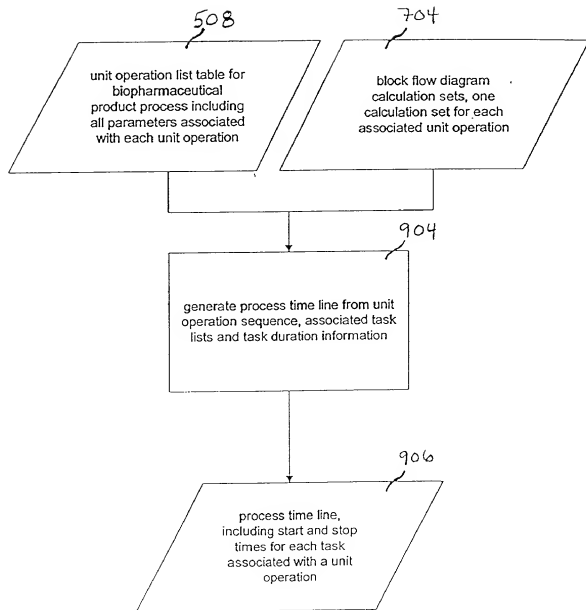


FIG. 9

# Sample Application of Process Design Cycles In Process Scheduling

## Microbial Fermentation Process (see unit operation list)

Duration	First Process Cycle		Second Process Cycle	
	Week	Day	Week	Day

Note: None of the unit operations in this process have more than 1 cycle per unit operation  
(see unit operation 8 in the mammalian cell culture process for an example of multiple cycles per unit operation)

Unit Operations 1-6 undergo three repetitive cycles per batch as a set before continuing with unit op 7

This translates to three runs on a fermentor with each harvest (unit op 5 & 6) being stored for pooling at unit op 7  
Associated with each fermentor run (unit op 4) are the previous steps for inoculation prep (unit ops 1-3)

### 1/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	1	Fri - Sat	2	Fri - Sat
2	Flask Growth	24 hrs	2	Sat - Sun	3	Sat - Sun
3	Seed Fermentation	24 hrs	2	Sun - Mon	3	Sun - Mon
4	Production Fermentation	24 hrs	2	Mon - Tue	3	Mon - Tue
5	Heat Exchange	1 hr	2	Tue	3	Tue
6	Centrifugation	1hr	2	Tue	3	Tue

### 2/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	2	Sun - Mon	3	Sun - Mon
2	Flask Growth	24 hrs	2	Mon - Tue	3	Mon - Tue
3	Seed Fermentation	24 hrs	2	Tue - Wed	3	Tue - Wed
4	Production Fermentation	24 hrs	2	Wed - Thu	3	Wed - Thu
5	Heat Exchange	1 hr	2	Thu	3	Thu
6	Centrifugation	1hr	2	Thu	3	Thu

### 3/3 fermentation cycles per batch

1	Inoculum Prep	24 hrs	2	Tue - Wed	3	Tue - Wed
2	Flask Growth	24 hrs	2	Wed - Thu	3	Wed - Thu
3	Seed Fermentation	24 hrs	2	Thu - Fri	3	Thu - Fri
4	Production Fermentation	24 hrs	2	Fri - Sat	3	Fri - Sat
5	Heat Exchange	1 hr	2	Sat	3	Sat
6	Centrifugation	1hr	2	Sat	3	Sat

Unit Operation 7 pools the harvests from the three fermentation cycles above

7	Pool Harvests	3 hr	3	Mon	4	Mon
---	---------------	------	---	-----	---	-----

Unit Operations 8-9 undergo three repetitive cycles per batch as set before continuing with unit operation 11  
This translates to three consecutive passes through cell disruptor (unit op 9) with its associated heat exchangers  
(unit op 8 & 10) at the inlet and the outlet of the cell disruptor

### 1/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

### 2/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

### 3/3 disruption cycles per batch

8	Heat Exchange					
9	Cell Disruption					
10	Heat Exchange	0.5 hr	3	Mon	4	Mon

FIG. 10

# Sample Application of Process Design Cycles in Process Scheduling

## Microbial Fermentation Process (see unit operation list)

Unit ops 11-12 undergo two repetitive cycles per batch as a set before continuing with unit op 13  
 This translates to two cycles of resuspending the cell lysate from the cell disruptor in a mild surfactant and reconcentrating the insoluble product to a paste by centrifugation

		First Process Cycle		Second Process Cycle	
	Duration	Week	Day	Week	Day
1/2 product washing cycles per batch					
11	Resuspension	0.5 hr	3 Mon	4 Mon	
12	Centrifugation	1 hr	3 Mon	4 Mon	
2/3 product washing cycles per batch					
11	Resuspension	0.5 hr	3 Mon	4 Mon	
12	Centrifugation	1 hr	3 Mon	4 Mon	
Unit ops 13-22 undergo only one cycle per unit operation each to the end of the process					
13	Resuspension	0.5 hr	3 Mon	4 Mon	
14	Buffer Exchange	2 hr	3 Mon	4 Mon	
15	Filtration	2 hr	3 Mon	4 Mon	
16	Liquid Chromatography	16 hrs	3 Mon - Tue	4 Mon - Tue	
17	Liquid Chromatography	4 hrs	3 Tue	4 Tue	
18	Buffer Exchange	2 hrs	3 Tue	4 Tue	
19	Liquid Chromatography	2 hrs	3 Wed	4 Wed	
20	Buffer Exchange	2 hrs	3 Wed	4 Wed	
21	Liquid Chromatography	2 hrs	3 Wed	4 Wed	
22	Filtration	2 hrs	3 Wed	4 Wed	

Locals and Units										Calculations									
Operation		Duration (Hrs)		Rel. Time Scale (Hrs)		Abs. Dose		Start		Finish									
		Qts.	AD	Adj.	Prop.	Exps.	Control	Start	End	Time	Time								
1 A. Inoculum Prep					15.5			0600PM	0630AM										
1	Set Up	3.0	0.0	3.0 Hrs															
2	Preinoculation	3.0	0.0	3.0 Hrs															
3	Inoculation	23.0	0.0	23.0 Hrs															
4	Clean Up	0.3	0.0	0.3 Hrs															
5	Subtotal	29.3	0.0	29.3 Hrs															
6	2 A. Flask Growth																		
7	Set Up	1.0	0.0	1.0 Hrs															
8	Preinoculation	1.0	0.0	1.0 Hrs															
9	Inoculation	23.0	0.0	23.0 Hrs															
10	Clean Up	0.3	0.0	0.3 Hrs															
11	Subtotal	25.3	0.0	25.3 Hrs															
12	3 A. 100% Fermentation																		
13	Set Up	1.0	0.0	1.0 Hrs															
14	Preinoculation	1.0	0.0	1.0 Hrs															
15	Inoculation	23.0	0.0	23.0 Hrs															
16	Clean Up	0.3	0.0	0.3 Hrs															
17	Subtotal	25.3	0.0	25.3 Hrs															
18	4 A. Production Fermentation																		
19	Set Up	1.0	0.0	1.0 Hrs															
20	Preinoculation	1.0	0.0	1.0 Hrs															
21	Inoculation	23.0	0.0	23.0 Hrs															
22	Clean Up	0.3	0.0	0.3 Hrs															
23	Subtotal	25.3	0.0	25.3 Hrs															
24	5 A. 100% Fermentation																		
25	Set Up	1.0	0.0	1.0 Hrs															
26	Preinoculation	1.0	0.0	1.0 Hrs															
27	Inoculation	23.0	0.0	23.0 Hrs															
28	Clean Up	0.3	0.0	0.3 Hrs															
29	Subtotal	25.3	0.0	25.3 Hrs															
30	6 A. Heat Exchange																		
31	Set Up	0.50	0.0	0.5 Hrs															
32	Preinoculation	0.50	0.0	0.5 Hrs															
33	Inoculation	1.0	0.0	1.0 Hrs															
34	Clean Up	0.50	0.0	0.5 Hrs															
35	Subtotal	2.50	0.0	2.5 Hrs															
36	7 A. Cont. Centrifugation																		
37	Set Up	1.00	0.0	1.0 Hrs															
38	Preinoculation	1.00	0.0	1.0 Hrs															
39	Inoculation	23.0	0.0	23.0 Hrs															
40	Clean Up	0.50	0.0	0.5 Hrs															
41	Subtotal	26.50	0.0	26.5 Hrs															
42	8 A. Cont. Centrifugation																		
43	Set Up	1.00	0.0	1.0 Hrs															
44	Preinoculation	1.00	0.0	1.0 Hrs															
45	Inoculation	23.0	0.0	23.0 Hrs															
46	Clean Up	0.50	0.0	0.5 Hrs															
47	Subtotal	26.50	0.0	26.5 Hrs															
48	9 A. Inoculum Prep																		
49	Set Up	1.0	0.0	1.0 Hrs															
50	Preinoculation	1.0	0.0	1.0 Hrs															
51	Inoculation	23.0	0.0	23.0 Hrs															
52	Clean Up	0.5	0.0	0.5 Hrs															
53	Subtotal	25.5	0.0	25.5 Hrs															
54	10 A. Inoculum Prep																		
55	Set Up	1.0	0.0	1.0 Hrs															
56	Preinoculation	1.0	0.0	1.0 Hrs															
57	Inoculation	23.0	0.0	23.0 Hrs															
58	Clean Up	0.5	0.0	0.5 Hrs															
59	Subtotal	25.5	0.0	25.5 Hrs															

15

14

13

12

11

10

9

8

7

6

5

4

3

2

1

0

-1

-2

-3

-4

-5

-6

-7

-8

-9

-10

-11

-12

-13

-14

-15

-16

-17

-18

-19

-20

-21

-22

-23

-24

-25

-26

-27

-28

-29

-30

-31

-32

-33

-34

-35

-36

-37

-38

-39

-40

-41

-42

-43

-44

-45

-46

-47

-48

-49

-50

-51

-52

-53

-54

-55

-56

-57

-58

-59

-60

-61

Process Time Use																			
Operation	Duration (Hrs.)		Rel. Time Scale (Hrs)		Abs. Dvrs.		Start		Finish	Time		Time		Time		Time		Time	
	Calc	Adj.	Adj.	Prep	Exec.	Compl.	Start	End		Time	Time	Time	Time	Time	Time	Time	Time	Time	Time
89 Inoculation	23.0	0.0	23.0 Hrs	34.5			06/03/96	06/03/96	06/04/96	02:30 PM									
90 Clean Up	23.0	0.0	0.3 Hrs	34.5			06/04/96	06/04/96	06/04/96	02:30 PM									
91 Subtotal	23.0		23.0 Hrs	34.5															
2 B Flask Growth																			
92 Set Up	1.0	0.0	1.0 Hrs	37.5															
93 Inoculation	23.0	0.0	23.0 Hrs	38.5															
94 Clean Up	23.0	0.0	0.3 Hrs	61.5															
95 Subtotal	25.0		25.0 Hrs	61.5															
3 B Seed Fermentation																			
96 Set Up	1.0	0.0	1.0 Hrs	66.5															
97 Fermentation	1.0	0.0	1.0 Hrs	61.5															
98 Harvest	0.5	0.0	0.5 Hrs	83.0															
99 CIP	1.0	0.0	1.0 Hrs	83.5															
100 SIP	1.0	0.0	1.0 Hrs	84.5															
101 Subtotal	25.0		25.0 Hrs	83.0															
4 B Production Fermentation																			
102 Set Up	1.0	0.0	1.0 Hrs	82.0															
103 Fermentation	21.0	0.0	21.0 Hrs	104.0															
104 SIP	1.0	0.0	1.0 Hrs	105.0															
105 Clean Up	2.0	0.0	2.0 Hrs	106.0															
106 Subtotal	25.0		25.0 Hrs	104.0															
5 B Inact Exchange																			
107 Set Up	0.50	0.0	0.5 Hrs	104.5															
108 Transfer	1.0	0.0	1.0 Hrs	105.0															
109 CIP	1.0	0.0	1.0 Hrs	106.0															
110 SIP	1.0	0.0	1.0 Hrs	107.0															
111 Subtotal	5.0		5.0 Hrs	105.0															
6 B Cont. Centrifuge																			
112 Set Up	1.00	0.0	1.0 Hrs	106.0															
113 Centrifugation	1.00	0.0	1.0 Hrs	106.1															
114 Wash	0.10	0.0	0.1 Hrs	106.1															
115 SIP	0.25	0.0	0.3 Hrs	106.4															
116 CIP	0.25	0.0	0.3 Hrs	106.4															
117 Clean Up	0.50	0.0	0.5 Hrs	107.0															
118 Subtotal	3.35		3.35 Hrs	106.1															
7 C Inoculum Prep																			
119 Set Up	1.0	0.0	1.0 Hrs	14.5															
120 Fermentation	1.0	0.0	1.0 Hrs	15.5															
121 SIP	0.25	0.0	0.3 Hrs	38.5															
122 Clean Up	0.25	0.0	0.3 Hrs	38.5															
123 Subtotal	2.50		2.50 Hrs	38.5															

Fig. 12B

Calculations

85.0 L 1.7 LPM = 0.50 Hrs

662.1 L @ 8.4 LPM = 1.00 Hrs

662.1 L @ 8.4 LPM = 1.00 Hrs

1.0 L @ 0.2 LPM = 0.10 Hrs

23.0 L @ 1.3 LPM = 0.25 Hrs

Process Unit Job												
Line	Operation	Duration (Hrs)		Rel. Time Scale (Hrs)	Abs. Durs		Start	Finish		Calculations		
		Calc.	Adj.		Pres.	Excc.		Comm.	Start		Time	End
110	2 C Flare Growth											
111	Set Up	1.0	0.0	1.0 Hrs	37.5			000000	12:30 PM	000000 01:30 PM		
112	Preinoculation	1.0	0.0	1.0 Hrs	38.5			000000	01:30 PM	000000 02:30 PM		
113	Incubation	20.0	0.0	21.0 Hrs	61.5			000000	01:30 PM	000000 01:30 PM		
114	Clean Up	0.3	0.0	0.3 Hrs				000000	01:30 PM	000000 01:30 PM		
115	Subtotal	25.0		25.0 Hrs	61.5			000000	01:30 PM	000000 01:30 PM		
120	3 C Seed Fermentation											
121	Set Up	1.0	0.0	1.0 Hrs	60.5			000000	11:30 AM	000000 12:30 PM		
122	Preinoculation	1.0	0.0	1.0 Hrs	61.5			000000	12:30 PM	000000 12:30 PM		
123	Fermentation	21.0	0.0	21.0 Hrs	82.5			000000	12:30 PM	000000 12:30 PM		
124	Harvest	0.5	0.0	0.5 Hrs	83.0			000000	12:30 PM	000000 12:30 PM		
125	CIP	1.0	0.0	1.0 Hrs				000000	11:30 AM	000000 11:30 AM		
126	Clean Up	0.4	0.0	0.4 Hrs				000000	12:30 PM	000000 12:30 PM		
127	Subtotal	23.9		23.9 Hrs	83.0			000000	12:30 PM	000000 12:30 PM		
130	4 C Production Fermentation											
131	Set Up	1.0	0.0	1.0 Hrs	83.0			000000	09:30 AM	000000 10:30 AM		
132	Preinoculation	1.0	0.0	1.0 Hrs	84.0			000000	10:30 AM	000000 11:30 AM		
133	Fermentation	21.0	0.0	21.0 Hrs	105.0			000000	10:30 AM	000000 10:30 AM		
134	CIP	1.0	0.0	1.0 Hrs				000000	10:30 AM	000000 10:30 AM		
135	Clean Up	0.4	0.0	0.4 Hrs				000000	10:30 AM	000000 10:30 AM		
136	Subtotal	23.4		23.4 Hrs	104.4			000000	10:30 AM	000000 10:30 AM		
140	6 C Heat Exchange											
141	Set Up	0.50	0.0	0.5 Hrs	104.5			000000	09:30 AM	000000 10:30 AM		
142	Preinoculation	1.0	0.0	1.0 Hrs	105.0			000000	10:30 AM	000000 11:30 AM		
143	Fermentation	1.0	0.0	1.0 Hrs	107.0			000000	10:30 AM	000000 11:30 AM		
144	CIP	2.0	0.0	2.0 Hrs	109.0			000000	11:30 AM	000000 12:30 PM		
145	Clean Up	0.50	0.0	0.5 Hrs				000000	10:30 AM	000000 10:30 AM		
146	Subtotal	5.0		5.0 Hrs	106.5			000000	11:30 AM	000000 12:30 PM		
150	6 C Cont. Cntr.Solids											
151	Set Up	1.00	0.0	1.0 Hrs	106.5			000000	09:30 AM	000000 10:30 AM		
152	Centrifugation	1.00	0.0	1.0 Hrs	108.5			000000	10:30 AM	000000 11:30 AM		
153	Wash	0.10	0.0	0.1 Hrs	108.6			000000	10:30 AM	000000 10:30 AM		
154	CIP	0.25	0.0	0.3 Hrs	109.1			000000	10:30 AM	000000 10:30 AM		
155	Clean Up	0.50	0.0	0.5 Hrs				000000	10:30 AM	000000 10:30 AM		
156	Sub Total	3.85		3.85 Hrs	106.1			000000	11:30 AM	000000 11:30 AM		
160	7 A. Heat Stabilization											
161	Set Up	1.00	0.0	1.0 Hrs	106.1			000000	09:30 AM	000000 10:30 AM		
162	Chilton	0.30	0.0	0.3 Hrs	106.8			000000	10:30 AM	000000 10:30 AM		
163	Wash	0.10	0.0	0.1 Hrs	107.6			000000	10:30 AM	000000 10:30 AM		
164	CIP	1.00	0.0	1.0 Hrs	109.6			000000	10:30 AM	000000 10:30 AM		
165	Clean Up	0.50	0.0	0.5 Hrs				000000	10:30 AM	000000 10:30 AM		
166	Subtotal	3.90		3.90 Hrs	107.6			000000	11:30 AM	000000 11:30 AM		
170	8 A. Heat Exchange											
171	Set Up	1.00	0.0	1.0 Hrs	107.6			000000	09:30 AM	000000 10:30 AM		
172	Chilton	0.30	0.0	0.3 Hrs	108.5			000000	10:30 AM	000000 10:30 AM		
173	Wash	0.10	0.0	0.1 Hrs	109.6			000000	10:30 AM	000000 10:30 AM		
174	CIP	1.00	0.0	1.0 Hrs	110.6			000000	10:30 AM	000000 10:30 AM		
175	Clean Up	0.50	0.0	0.5 Hrs				000000	10:30 AM	000000 10:30 AM		
176	Subtotal	3.90		3.90 Hrs	107.6			000000	11:30 AM	000000 11:30 AM		

FIG. 12C

Process Time Line										Rel. Time Scale (Hrs)										Calculations									
Operation (Hrs)										Start										Finish									
Calc. ADJ.										Date										Time									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									
Calc. ADJ.										Start										Finish									



Process Time Line										
Operation	Duration (Hrs.)		Rel. Time-Start (Hrs.)		Abs. Date		Start		Calculations	
	Circ.	Adj.	Prep	Exec.	Comp.	Start	End	Time		
								Time		Time
226			15.5			06/03/96	06/03 AM			
9 C Homogenization										
227	Set Up	0.00	0.0	0.0	Hrs	4:50	4:50	06/07/96	02:27 PM	
228	Set Up	0.08	0.0	0.7	Hrs	11:11		06/07/96	02:27 PM	
229	CIP	0.00	0.0	0.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
230	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
231	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
232	Clean Up	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
233	Sub Total	3.7		3.7	Hrs	11:11		06/07/96	02:27 PM	
10 C Heat Exchange										
234	Set Up	0.00	0.0	0.0	Hrs	4:50	4:50	06/07/96	02:27 PM	
235	Transfer	0.30	0.0	0.3	Hrs	11:11		06/07/96	02:27 PM	
236	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
237	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
238	Clean Up	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:27 PM	
239	Sub Total	3.3		3.3	Hrs	11:11		06/07/96	02:27 PM	
11 A Resubilization										
240	Set Up	1.00	0.0	1.0	Hrs	10:59		06/07/96	11:52 AM	
241	Disin	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 AM	
242	Agitate	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 AM	
243	CIP	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
244	CIP	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
245	Clean Up	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
246	Sub Total	2.0		2.0	Hrs	10:59		06/07/96	11:52 PM	
12 A Cont. Cans/Solids										
247	Set Up	1.00	0.0	1.0	Hrs	10:59		06/07/96	11:52 PM	
248	Disin	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
249	Agitate	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
250	CIP	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
251	CIP	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
252	Clean Up	0.00	0.0	0.0	Hrs	10:59		06/07/96	11:52 PM	
253	Sub Total	1.0		1.0	Hrs	10:59		06/07/96	11:52 PM	
11 B Resubilization										
254	Set Up	0.00	0.0	0.0	Hrs	4:50	4:50	06/07/96	02:28 PM	
255	Disin	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:28 PM	
256	Agitate	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:28 PM	
257	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
258	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
259	Clean Up	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
260	Sub Total	3.0		3.0	Hrs	11:11		06/07/96	02:28 PM	
12 B Cont. Cans/Solids										
261	Set Up	1.00	0.0	1.0	Hrs	11:11		06/07/96	02:28 PM	
262	Disin	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:28 PM	
263	Agitate	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:28 PM	
264	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
265	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
266	Clean Up	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:28 PM	
267	Sub Total	3.0		3.0	Hrs	11:11		06/07/96	02:28 PM	
13 A Resubilization										
268	Set Up	1.00	0.0	1.0	Hrs	11:11		06/07/96	02:13 PM	
269	Disin	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:13 PM	
270	Agitate	0.00	0.0	0.0	Hrs	11:11		06/07/96	02:13 PM	
271	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:13 PM	
272	CIP	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:13 PM	
273	Clean Up	1.00	0.0	1.0	Hrs	11:11	11:11	06/07/96	02:13 PM	
274	Sub Total	3.0		3.0	Hrs	11:11		06/07/96	02:13 PM	
13 B Resubilization										
275	Set Up	1.00	0.0	1.0	Hrs	11:05		06/07/96	02:30 PM	
276	Disin	0.00	0.0	0.0	Hrs	11:05		06/07/96	02:30 PM	
277	Agitate	0.00	0.0	0.0	Hrs	11:05		06/07/96	02:30 PM	
278	CIP	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
279	CIP	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
280	Clean Up	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
281	Sub Total	3.0		3.0	Hrs	11:05		06/07/96	02:30 PM	
13 C Resubilization										
282	Set Up	1.00	0.0	1.0	Hrs	11:05		06/07/96	02:30 PM	
283	Disin	0.00	0.0	0.0	Hrs	11:05		06/07/96	02:30 PM	
284	Agitate	0.00	0.0	0.0	Hrs	11:05		06/07/96	02:30 PM	
285	CIP	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
286	CIP	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
287	Clean Up	1.00	0.0	1.0	Hrs	11:05	11:05	06/07/96	02:30 PM	
288	Sub Total	3.0		3.0	Hrs	11:05		06/07/96	02:30 PM	

FIG. 12E

Process Time Line										Rel. Time Scale (hrs.)		Alt. Crs.		Start		Finish		Calculations	
Duration (hrs.)		Prep	Exct.	Comp.	Start	End	Start	End	Date	Time	Date	Time							
Cyle	AD	Adj.	103	110.5	111.0	121.0	120.0	120.0	120.0	06/20/94	06/20/94	06/20/94	06/20/94						
219	Set Up	1.0	0.0	1.0	110.5	4.85	4.85	4.85	4.85	000766	000766	000766	000766					60.7 L @ 2.0 LPM = 5.0 Hrs. 25.50 Hrs.	
220	Run	0.5	0.0	0.5	111.0	4.80	4.80	4.80	4.80	000766	000766	000766	000766						
221	Dilution	0.5	0.0	0.5	111.0	4.80	4.80	4.80	4.80	000766	000766	000766	000766						
222	Wash	0.5	0.0	0.5	111.0	4.80	4.80	4.80	4.80	000766	000766	000766	000766						
223	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
224	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
225	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
226	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
227	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
228	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
229	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
230	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
231	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
232	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
233	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
234	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
235	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
236	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
237	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
238	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
239	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
240	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
241	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
242	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
243	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
244	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
245	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
246	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
247	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
248	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
249	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
250	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
251	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
252	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
253	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
254	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
255	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
256	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
257	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
258	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
259	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
260	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
261	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
262	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
263	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
264	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
265	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
266	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
267	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
268	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
269	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
270	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
271	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
272	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
273	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
274	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
275	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
276	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
277	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
278	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
279	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
280	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
281	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
282	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
283	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
284	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
285	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
286	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
287	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
288	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
289	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
290	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
291	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
292	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
293	Dilution	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
294	Wash	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
295	Set Up	1.0	0.0	1.0	121.0	120.0	5.27	5.27	5.27	000766	000766	000766	000766						
296	Run	0.5	0.0	0.5	121.0	120.0	5.27	5.27	5.27	000766	0007								

FIG. 12F

Process Time Line																			
Duration (Hrs.)																			
Rel. Time Scale (Hrs.)																			
Calc. AD																			
Cate. AD																			
Adj.																			
Prep																			
Exec. Compl.																			
Start																			
End																			
Days																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			
Time																			
Date																			

Operation	Duration (hrs)		Rel. Time State (hrs)		Abs. Dhrs		Start		Finish		Calculations	
	Cals. AD	Asp.	Prep	Exec.	Compl.	Start	End	Date	Time	Date		
416	1.0	0.0		15.5				000096	0300 AM			
418	2.1	0.0		143.8				000096	1154 PM	000096	1254 AM	
417				140.8								
419												
420												
421												
422												
423												
424												
425												
426												
427												
428												
429												
430												
431												
432												
433												
434												
435												
436												
437												
438												
439												
440												
441												
442												
443												
444												
445												
446												
447												
448												
449												
450												
451												
452												
453												
454												
455												
456												
457												
458												
459												
460												
461												
462												
463												
464												
465												
466												
467												
468												
469												
470												
471												
472												
473												
474												
475												
476												
477												
478												
479												
480												
481												
482												
483												
484												
485												
486												
487												
488												
489												
490												
491												
492												
493												
494												
495												
496												
497												
498												
499												
500												

FIG. 12H

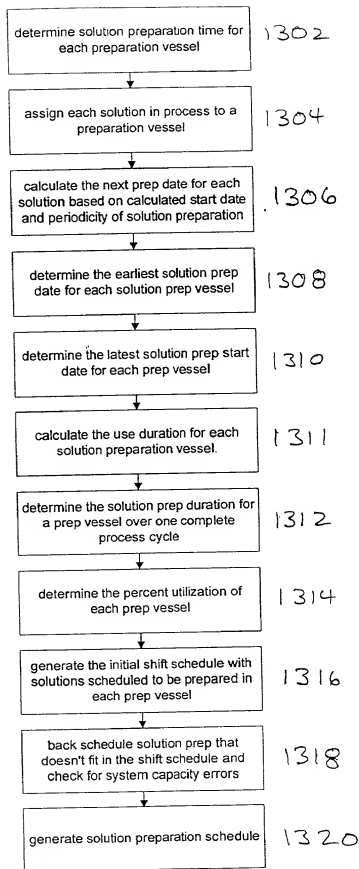
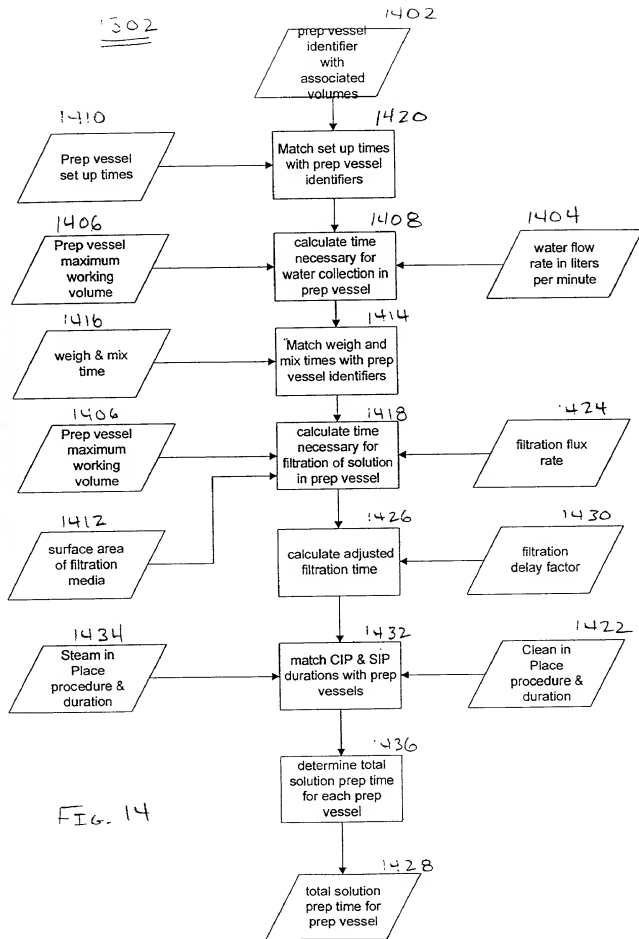


FIG. 13



[illegible]

1402 1406 1410 1404 1412 1424 1506 1422 1428 1434

5  
H  
L

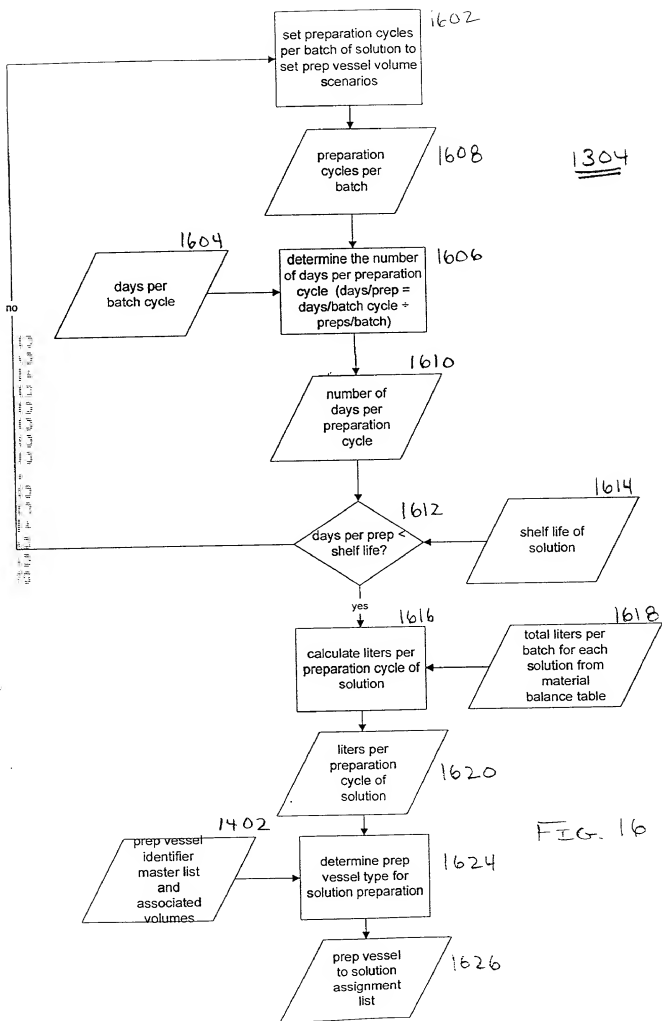


FIG. 16



Solution Prep Campaign Format

162.6

Soln. ID	Storage Cont.		Soln. Prep Format			Solution Prep Cycles			Liters/ Prep	Days/ Bat. Cy	Days/ Prep	Shelf Days	Shelf Check	101 102 103 104 105 106 107									
	RT	4C	XP	MOD	BOD	BIA	Liters/ Batch	Preps/ Batch						0.5	1	2	4	10	20	50	100		
1 S-0101	X	X		0	X	0	1,665.50	1	1,665.50	7	7	56	OK										
2 S-0102	X	X		0	X	0	1,665	1	1,665	7	7	180	OK										
3 S-0103	X	X		0	X	0	1,665	1	1,665	7	7	180	OK										
4 S-0104	X	X		0	X	0	8.25	1	8.25	7	7	56	OK										
5 S-0105	X	X		0	X	0	8.25	1	8.25	7	7	56	OK										
6 S-0106	X	X		0	X	0	560.61	1	560.61	7	7	56	OK										
7 S-0107	X	X		0	X	0	125.93	1	125.93	7	7	56	OK										
8 S-0108	X	X		0	X	0	177.41	1	177.41	7	7	56	OK										
9 S-0109	X	X		0	X	0	22.16	1	22.16	7	7	56	OK										
10 S-0110	X	X		0	X	0	56.52	1	56.52	7	7	56	OK										
11 S-0111	X	X		0	X	0	113.03	1	113.03	7	7	56	OK										
12 S-0112	X	X		0	X	0	1,812.45	1	1,812.45	7	7	56	OK										
13 S-0113	X	X		0	X	0	574.10	1	574.10	7	7	56	OK										
14 S-0114	X	X		0	X	0	248.83	1	248.83	7	7	56	OK										
15 S-0115	X	X		0	X	0	497.65	1	497.65	7	7	56	OK										
16 S-0116	X	X		0	X	0	109.80	1	109.80	7	7	56	OK										
17 S-0117	X	X		0	X	0	497.65	1	497.65	7	7	56	OK										
18 S-0118	X	X		0	X	0	292.79	1	292.79	7	7	56	OK										
19 S-0119	X	X		0	X	0	109.80	1	109.80	7	7	56	OK										
20 S-0120	X	X		0	X	0	62.58	1	62.58	7	7	56	OK										
21 S-0121	X	X		0	X	0	0.00	1	0.00	7	7	56	OK										
22 S-0122	X	X		0	X	0	0.00	1	0.00	7	7	56	OK										

162.6 160.4 161.4 161.0 160.6

170.4

Fig. 17

## Solution Prep Campaign Format

1626

Soln. ID	Tank Assignment					Solution Prep Schedule					Tank Enl						
	108	109	110	111		Initial Assign.	Final Assign.	Required By	Back Days	Avail. By	Hold Days	In/L Start	Float Days	Final Start	Next Prep	Prep. Hrs.	101
1 S-0101					111	111	111	06/03/96	1	06/31/96	2	06/29/96	0	06/29/96	06/05/96		4
2 S-0102					102	102	102	06/05/96	1	06/04/96	2	06/31/96	0	06/31/96	06/07/96		4
3 S-0103					102	102	102	06/05/96	1	06/04/96	2	06/31/96	0	06/31/96	06/07/96		4
4 S-0104					104	104	104	06/05/96	1	06/04/96	2	06/31/96	0	06/31/96	06/07/96		4
5 S-0105					104	104	104	06/05/96	1	06/04/96	2	06/31/96	0	06/31/96	06/07/96		4
6 S-0106			110		110	110	110	06/07/96	1	06/06/96	2	06/04/96	0	06/04/96	06/11/96		4
7 S-0107	108				108	108	108	06/11/96	1	06/10/96	2	06/07/96	0	06/07/96	06/14/96		4
8 S-0108	108				108	108	108	06/11/96	1	06/10/96	2	06/07/96	0	06/07/96	06/14/96		4
9 S-0109					106	106	106	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
10 S-0110					107	107	107	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
11 S-0111					108	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
12 S-0112				111	111	111	111	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
13 S-0113					110	110	110	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
14 S-0114	108				108	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
15 S-0115					109	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
16 S-0116				109	109	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
17 S-0117	108				108	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
18 S-0118					109	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
19 S-0119					109	109	109	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
20 S-0120	108				108	108	108	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
21 S-0121					107	107	107	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4
22 S-0122					0	0	0	06/12/96	1	06/11/96	2	06/07/96	0	06/07/96	06/14/96		4

Min. 05/29/96 06/14/96

Min.

06/03/96

Min

06/12/96

Max

0

Sat

0

Sun

1726 1728

1724

176 10

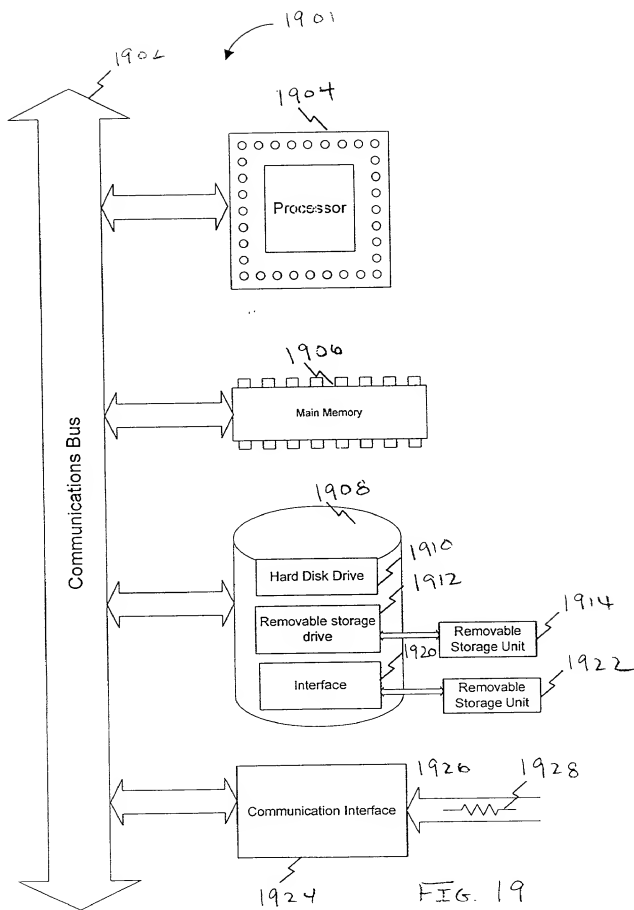


FIG. 19

1306

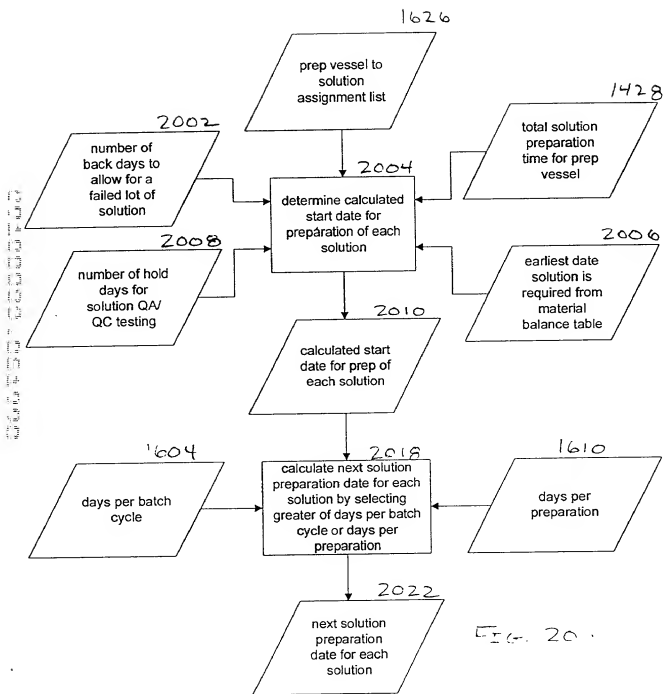


FIG. 20.

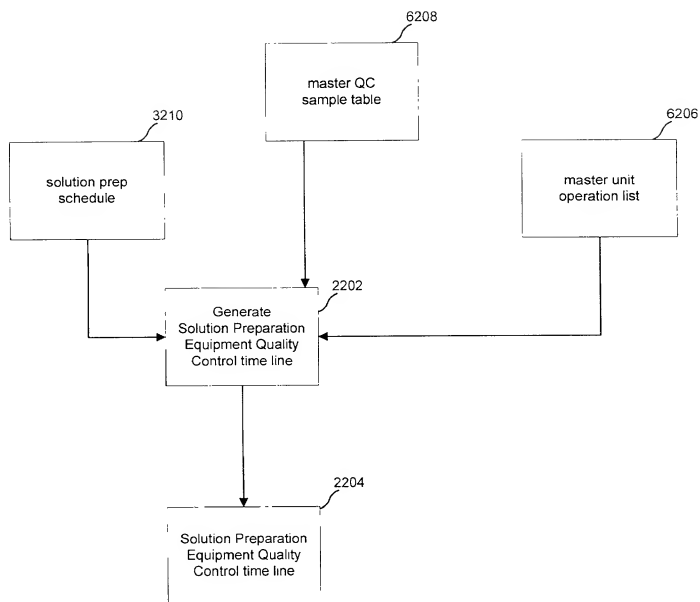
2102

2104

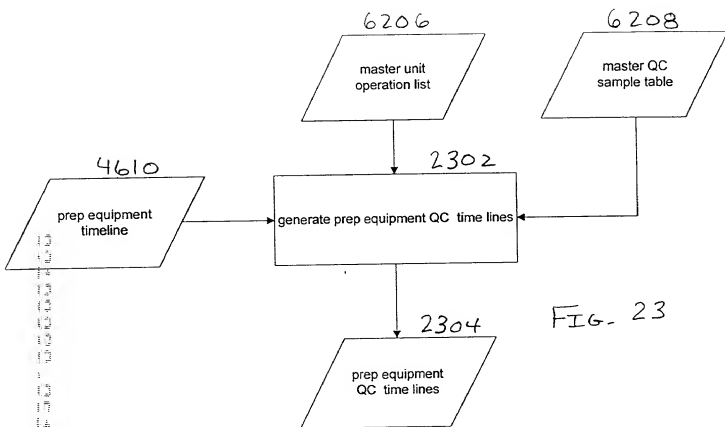
2106

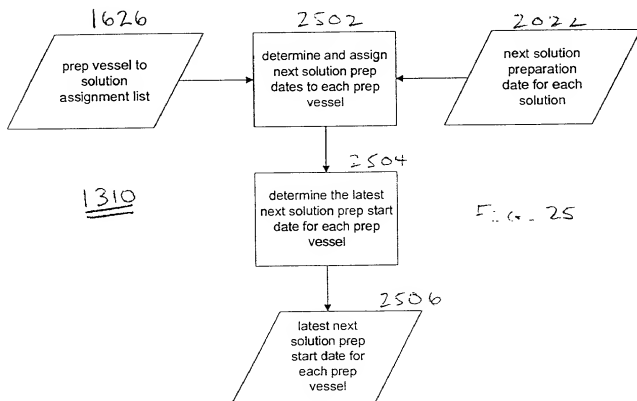
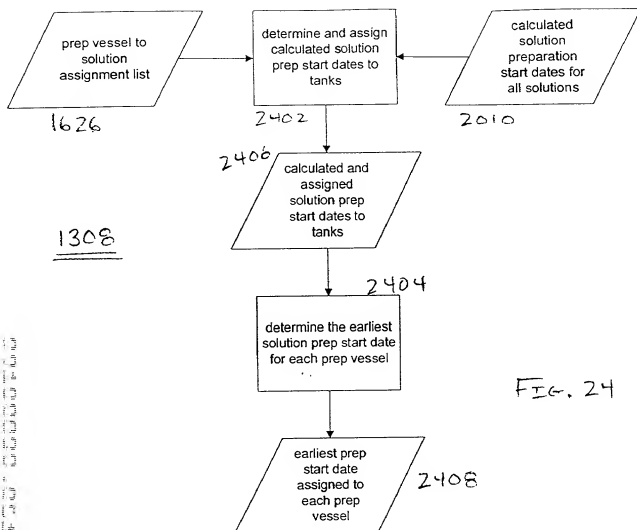
Category/Assay	Code	Man Hour			Disp. Material
		Set Up	Per Sample	Clean Up	
1 Environmental	E-1	0.5	0.1	0.5	
2 Temperature	E-2	0.5	0.1	0.5	
3 Humidity	E-3	0.5	0.2	0.5	
4 Particle Count					
5					
6 Analytical					
7 Visual	AV-1	0.25	0.2	0.5	
8 Certificate of Analysis	AV-2	0.25	0.05	0.25	
9 Appearance					
10 Chemical	AC-1	0.5	0.1	0.5	
11 Solubility	AC-2	0.25	0.05	0.25	
12 pH	AC-3	0.25	0.1	0.25	
13 Osmolality	AC-4	0.5	0.2	0.5	
14 Water Content (by Karl Fischer)	AC-5	1	0.25	1	
15 Key Element Analysis (by ICP Atomic Adsorption Spectroscopy)	AC-6	1	0.25	1	
16 GC/Mass Spec					
17 Biochemical					
18 DNA	AB-1	0.5	0.1	0.5	
19 DNA Fluorochrome Stain					
20 Protein	AB-2	0.5	0.1	0.5	
21 Hemoglobin	AB-3	1	0.2	1	
22 Electrophoretic Profiles by SDS-PAGE	AB-4	0.25	0.1	0.25	
23 A280	AB-5	0.5	0.1	0.5	
24 Bradford Assay	AB-6	1	0.25	1	
25 Amino Acid Analysis by HPLC		0.5	0.1	0.5	
26 Endotoxin	AB-7				
27 Gel Clot LAL					
28 Immunological	AI-1	1	0.1	1	
29 ELISA	AI-2	1.5	0.2	1.5	
30 Western Blots					
31 Activity	AA-1	1	0.1	1	
32 Chromagenic Substrate Assays					
33					
34 In Vitro Biological	VB-1	0.5	0.2	0.5	
35 Microbiological	VB-2	0.5	0.2	0.5	
36 Mycoplasma (Barile Method)	VB-3	0.5	0.2	0.5	
37 Bacteriophage (Screened)	VB-4	1	0.2	1	
38 Cell Passage Test		2	0.2	1	
39 Adventitious viral Agents	VB-5	2	0.2	1	
40 CPE	VB-6	2	0.2	1	
41 BVD	VB-7	2	0.2	1	
42 P13	VB-8	2	0.2	1	
43 IBR					
44 Virus Neutralization Titers (9CFR)	VB-9	2	0.2	1	
45 BVD	VB-10	2	0.2	1	
46 P13	VB-11	2	0.2	1	
47 IBR	VB-12	2	0.2	1	
48 Tritiated Thymidine Uptake in Mouse Cells	VB-13	1	0.2	1	
49 General Safety Test (Guinea Pigs)					
50					
51					

FIG. 21



**FIG. 22**







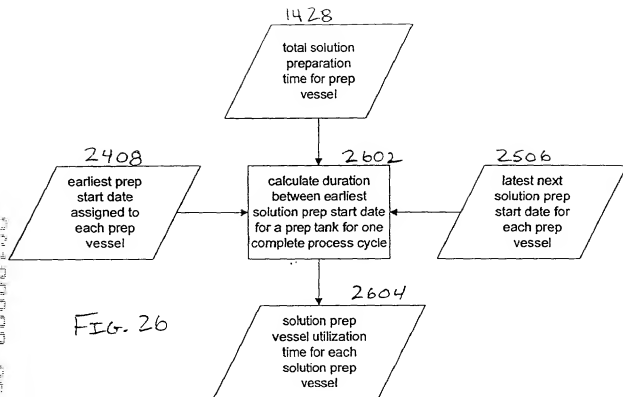
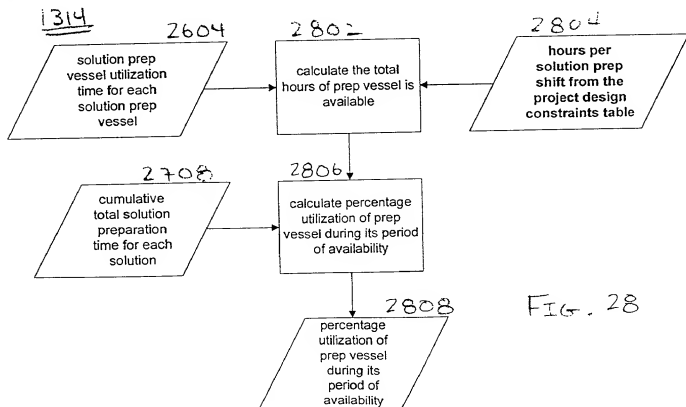
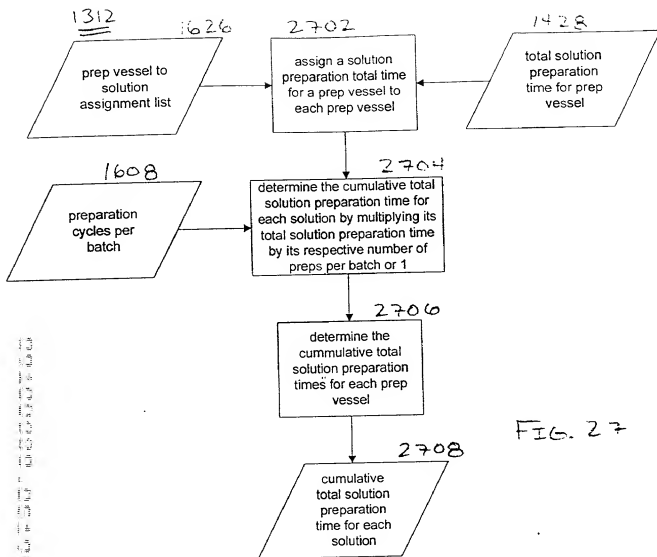
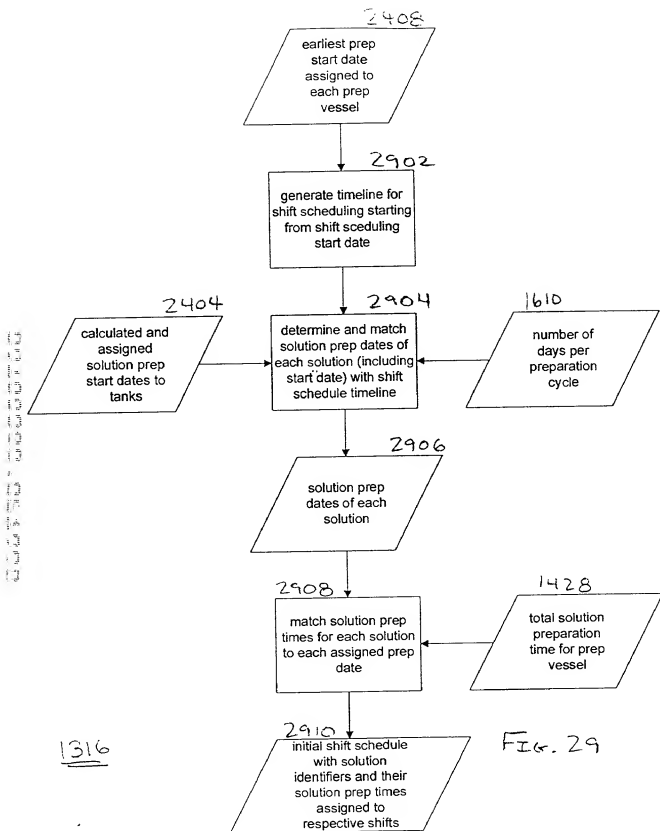


FIG. 26





1318

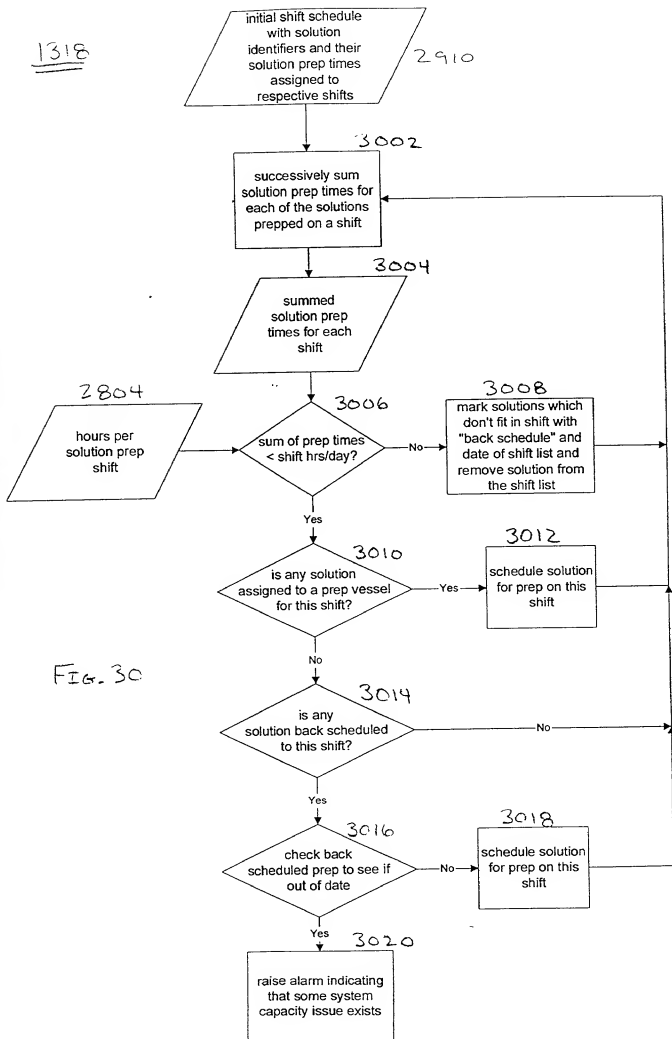


FIG. 30

[illegible]

9062 01-1 2010

31

1320

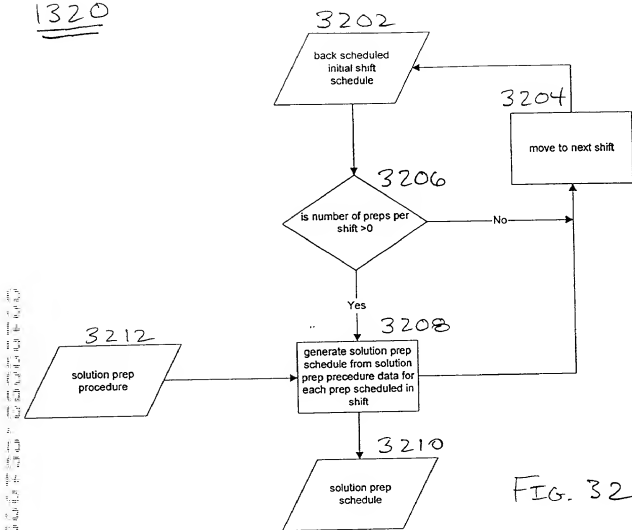
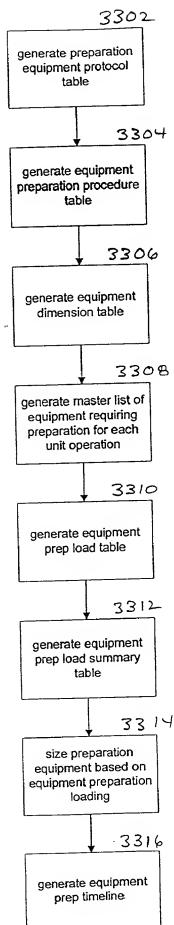
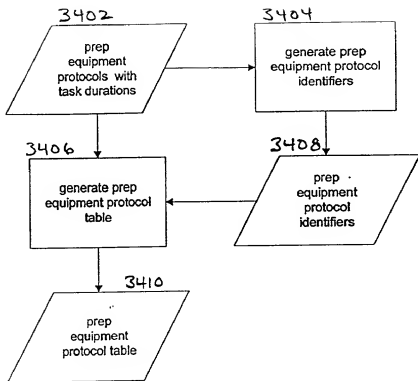


FIG. 32

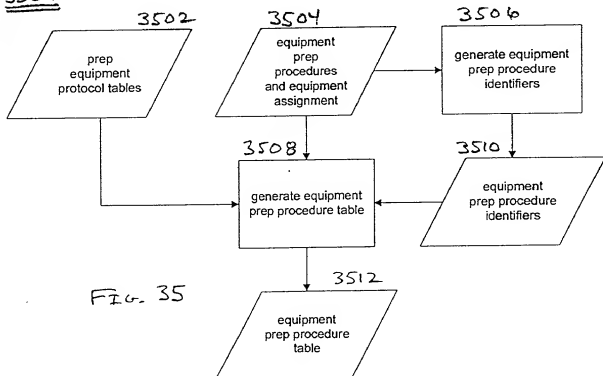
FIG. 33



3302



3304





Prep Equipment Protocol - Bench Sink

3408 3602 3604

Cycler Code	Minutes/Cycle										Total
	Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	Hold/ Dry	
		NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW			
1 BS-1	5	2	2	5	Alconox	0.5	2	2	2		20
2 BS-2	5	2	2	5	Alconox	0.5	2	2	2		20
3 BS-3	5	2	2	5	Alconox	0.5	2	2	2		20
4 BS-4	5	2	2	5	Alconox	0.5	2	2	2		20
5 BS-5	5	2	2	5	Alconox	0.5	2	2	2		20

FIG. 36A

# Prep Equipment Protocol - Wash Station

3408

Protocol	Cycle Code	Minutes/Cycle									Total
		Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	
			NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW		
1	WS-1	5	2	2	5	Alconox	0.5	2	2	2	15
2	WS-2	5	2	2	5	Alconox	0.5	2	2	2	15
3	WS-3	5	2	2	5	Alconox	0.5	2	2	2	15
4	WS-4	5	2	2	5	Alconox	0.5	2	2	2	15
5	WS-5	5	2	2	5	Alconox	0.5	2	2	2	15

FIG. 36B

Prep Equipment Protocol - Glassware Washer

Minutes/Cycle												
Cycle Code	Load	Pre Wash Rinse		Detergent Wash			Post Wash Rinse		Final Rinse	Unload	Total	
		NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW				
1 GW-1	15	2	2	5	Alconox	0.5	2	2	2	10	40	
2 GW-2	15	2	2	5	Alconox	0.5	2	2	2	10	40	
3 GW-3	15	2	2	5	Alconox	0.5	2	2	2	10	40	
4 GW-4	15	2	2	5	Alconox	0.5	2	2	2	10	40	
5 GW-5	15	2	2	5	Alconox	0.5	2	2	2	10	40	

FIG. 36C

# Prep Equipment Protocol - Glassware Dryer

3408

	Cycle Code	Load	Heat Up Minutes	Dry		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	DO-1	10	30	250	40	30	10	120
2	DO-2	10	30	250	25	30	10	105
3	DO-3	10	30	250	25	30	10	105
4	DO-4	10	30	250	25	30	10	105
5	DO-5	10	30	250	25	30	10	105

3618

3620

3622

3624

3626

3628

FIG. 36D

# Prep Equipment Protocol - Carboy Washer

1-55-11 3408

Minutes/Cycle										
Load	Pre Wash Rinse		Detergent			Post Wash Rinse		Final Rinse	Unload	Total
	NPHW	NPCW	Minutes	Reagent	Gm/CF	NPHW	NPCW			
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15
15	2	2	5	Alconox	0.5	2	2	2	15	15

FIG. 36E

Prep Equipment Protocol - Carboy Dryer

3408

	Cycle Code	Load	Heat Up Minutes	Dry		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	CD-1	10	30	250	40	30	10	100
2	CD-2	10	30	250	25	30	10	85
3	CD-3	10	30	250	25	30	10	85
4	CD-4	10	30	250	25	30	10	85
5	CD-5	10	30	250	25	30	10	85

FIG. 36F

3606 3608 3610 3612 3614 3616

Cycles											
SS-1				SS-2				SS-3			
Pres. (Bar)	Minutes To Ach.	No. of Cycles	Subt.	Pres. (Bar)	Minutes To Ach.	Minutes To Hold	No. of Cycles	Pres. (Bar)	Minutes To Ach.	Minutes To Hold	No. of Cycles
1	Load		20								
2											
3	Pre Sterilization										
4	Deep Vacuum	15	1	16							
5	Vacuum/Steam Pulse										
6	Vacuum				3	0	9		3	0	9
7	Steam			1	2	0	9		2	0	9
8	Subtotal		18						18	0	9
9									45		45
10	Sterilization										
11	Steam				20	40	1		20	40	1
12	Steam/Air										
13	Subtotal		60						60		60
14											
15	Cooling										
16	Dried Air Cooling										
17	Indirect Jacket Cooling	0	40	0	40	0	1		40	0	1
18	Overpressure								40	0	1
19	Subtotal		40						40		80
20											
21	Drying										
22	Fast Exhaust	0	20	5	25				20	5	1
23	Slow Exhaust										
24	Deep Vacuum										
25	Vacuum Pulse								30		
26	Heat										
27	Heated Pressure										
28	Subtotal		25						30		25
29											
30	Unload								20		20
31											
32	Total Minutes		161						195		230
33	Total Hours		2.7						3.3		3.8

Fig. 366

Prep Equipment Protocol - Dry Heat Sterilizer

3400

	Cycle Code	Load	Heat Up Minutes	Sterilization		Cool Minutes	Unload	Total
				Temp (C)	Minutes			
1	SO-1	15	30	250	40	30	15	130
2	SO-2	15	30	250	25	30	15	115
3	SO-3	15	30	250	25	30	15	115
4	SO-4	15	30	250	25	30	15	115
5	SO-5	15	30	250	25	30	15	115

FIG. 36H



Pre-Equipment Protocol - Equipment Prep Procedures

3706

3702

3704

			EPC1	EPC2	EPC3	EPC4	EPC5	EPC6	EPC7
1	Initial Rinse								
2									
3	Bench Sink - 1								
4	Procedure	PHrs.	BS-1	BS-1	BS-2	BS-1			
5	Duration	PHrs.	0.33	0.33	0.33	0.33			
6	Hold/Dry	PHrs.	0	0	0				
7	Subtotal	PHrs.	0.33	0.33	0.33	0.33	0.00	0.00	0.00
8	Cumulative	PHrs.	0.33	0.33	0.33	0.33	0.00	0.00	0.00
9									
10	Wash Station - 1								
11	Procedure	PHrs.					WS-1	WS-1	
12	Duration	PHrs.					0.25	0.25	
13	Hold/Dry	PHrs.							
14	Subtotal	PHrs.	0.00	0.00	0.00	0.00	0.25	0.25	0.00
15	Cumulative	PHrs.	0.33333	0.33333	0.33333	0.33333	0	0	0
16									
17	Cleaning								
18									
19	Bench Sink - 1								
20	Procedure	PHrs.	BS-3	BS-3	BS-4				
21	Duration	PHrs.	0.33	0.33	0.33				
22	Hold/Dry	PHrs.							
23	Subtotal	PHrs.	0.33	0.33	0.33	0.00	0.00	0.00	0.00
24	Cumulative	PHrs.	0.66667	0.66667	0.66667	0.33333	0	0	0
25									
26	Glassware Washer - 1								
27	Procedure	PHrs.				GW-1			
28	Duration	PHrs.				0.67			
29	Hold/Dry	PHrs.							
30	Subtotal	PHrs.	0.00	0.00	0.00	0.67	0.00	0.00	0.00
31	Cumulative	PHrs.	0.66667	0.66667	0.66667	1	0	0	0
32									
33	Glassware Dryer - 1								
34	Procedure	PHrs.	GD-1	GD-1	GD-2	GD-3			
35	Duration	PHrs.	2.00	2.00	1.75	1.75			
36	Hold/Dry	PHrs.							
37	Subtotal	PHrs.	2.00	2.00	1.75	1.75	0.00	0.00	0.00
38	Cumulative	PHrs.	2.66667	2.66667	2.41667	2.75	0	0	0
39									
40	Carboy Washer - 1								
41	Procedure	PHrs.					CW-1	CW-1	
42	Duration	PHrs.					0.25	0.25	
43	Hold/Dry	PHrs.							
44	Subtotal	PHrs.	0.00	0.00	0.00	0.00	0.25	0.25	0.00
45	Cumulative	PHrs.	2.66667	2.66667	2.41667	2.75	0.25	0.25	0
46									
47	Carboy Dryer - 1								
48	Procedure	PHrs.					CD-1	CD-1	
49	Duration	PHrs.					1.67	1.67	
50	Hold/Dry	PHrs.							
51	Subtotal	PHrs.	0.00	0.00	0.00	0.00	1.67	1.67	0.00
52	Cumulative	PHrs.	2.66667	2.66667	2.41667	2.75	1.91667	1.91667	0
53									
54	Prep								
55									
56	Staffing		2	2	2	2	2	2	2
57									
58	Preassembly								
59	Man Hours	MHrs.		1					
60	Procedure Hours			0.5					

FIG. 37A

Prep Equipment Protocol - Equipment Prep Procedures

			EPC1	EPC2	EPC3	EPC4	EPC5	EPC6	EPC7
61	Cummulative	PHrs.	2.66667	3.16667	2.41667	2.75	1.91667	1.91667	0
62									
63	Wrap								
64	Man Hours	MHrs.	1.5	1.5	1.5	1.5	1.5	1.5	1.5
65	Procedure Hours		0.75	0.75	0.75	0.75	0.75	0.75	0.75
66	Cummulative	PHrs.	3.41667	3.91667	3.16667	3.5	2.66667	2.66667	0.75
67									
68	Sterilization								
69									
70	Autoclave - 1								
71	Procedure		SS-1	SS-1	SS-1	SS-1	SS-2		SS-3
72	Duration	PHrs.	2.68	2.68	2.68	2.68	3.25		3.83
73	Hold/Dry	PHrs.							
74	Subtotal	PHrs.	2.68	2.68	2.68	2.68	3.25	0.00	3.83
75	Cummulative	PHrs.	6.10	6.60	5.85	6.18	5.92	2.67	4.58
76									
77	Dry Heat - 1								
78	Procedure							SO-1	
79	Hours/Load	PHrs.						2.17	
80	Hold/Dry	PHrs.							
81	Subtotal	PHrs.	0.00	0.00	0.00	0.00	0.00	2.17	0.00
82	Cummulative	PHrs.	6.10	6.60	5.85	6.18	5.92	4.83	4.58
83									
84	Total		6.10	6.60	5.85	6.18	6.17	5.08	4.58
85									
86	Max		2.68	2.68	2.68	2.68	3.25	2.17	3.83

Fig. 378

3306

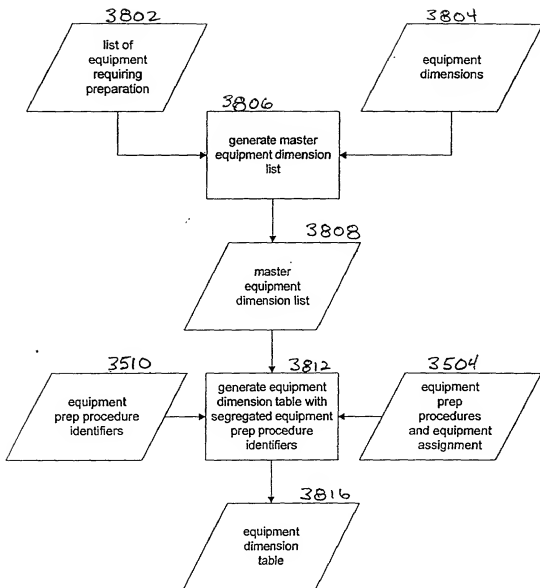


FIG. 38

3902

DPC-1		DPC-2		DPC-3		DPC-4		DPC-5		DPC-6		DPC-7		DPC-8		DPC-9		DPC-10		DPC-11		DPC-12		DPC-13		DPC-14		DPC-15		DPC-16		DPC-17		DPC-18		DPC-19		DPC-20		DPC-21		DPC-22		DPC-23		DPC-24		DPC-25		DPC-26		DPC-27		DPC-28		DPC-29		DPC-30		DPC-31		DPC-32		DPC-33		DPC-34		DPC-35		DPC-36		DPC-37		DPC-38		DPC-39		DPC-40		DPC-41		DPC-42		DPC-43		DPC-44		DPC-45		DPC-46		DPC-47		DPC-48		DPC-49		DPC-50		DPC-51		DPC-52		DPC-53		DPC-54		DPC-55		DPC-56		DPC-57		DPC-58		DPC-59		DPC-60		DPC-61		DPC-62		DPC-63		DPC-64		DPC-65		DPC-66		DPC-67		DPC-68		DPC-69		DPC-70		DPC-71		DPC-72		DPC-73		DPC-74		DPC-75		DPC-76		DPC-77		DPC-78		DPC-79		DPC-80		DPC-81		DPC-82		DPC-83		DPC-84		DPC-85		DPC-86		DPC-87		DPC-88		DPC-89		DPC-90		DPC-91		DPC-92		DPC-93		DPC-94		DPC-95		DPC-96		DPC-97		DPC-98		DPC-99		DPC-100		DPC-101		DPC-102		DPC-103		DPC-104		DPC-105		DPC-106		DPC-107		DPC-108		DPC-109		DPC-110		DPC-111		DPC-112		DPC-113		DPC-114		DPC-115		DPC-116		DPC-117		DPC-118		DPC-119		DPC-120		DPC-121		DPC-122		DPC-123		DPC-124		DPC-125		DPC-126		DPC-127		DPC-128		DPC-129		DPC-130		DPC-131		DPC-132		DPC-133		DPC-134		DPC-135		DPC-136		DPC-137		DPC-138		DPC-139		DPC-140		DPC-141		DPC-142		DPC-143		DPC-144		DPC-145		DPC-146		DPC-147		DPC-148		DPC-149		DPC-150		DPC-151		DPC-152		DPC-153		DPC-154		DPC-155		DPC-156		DPC-157		DPC-158		DPC-159		DPC-160		DPC-161		DPC-162		DPC-163		DPC-164		DPC-165		DPC-166		DPC-167		DPC-168		DPC-169		DPC-170		DPC-171		DPC-172		DPC-173		DPC-174		DPC-175		DPC-176		DPC-177		DPC-178		DPC-179		DPC-180		DPC-181		DPC-182		DPC-183		DPC-184		DPC-185		DPC-186		DPC-187		DPC-188		DPC-189		DPC-190		DPC-191		DPC-192		DPC-193		DPC-194		DPC-195		DPC-196		DPC-197		DPC-198		DPC-199		DPC-200		DPC-201		DPC-202		DPC-203		DPC-204		DPC-205		DPC-206		DPC-207		DPC-208		DPC-209		DPC-210		DPC-211		DPC-212		DPC-213		DPC-214		DPC-215		DPC-216		DPC-217		DPC-218		DPC-219		DPC-220		DPC-221		DPC-222		DPC-223		DPC-224		DPC-225		DPC-226		DPC-227		DPC-228		DPC-229		DPC-230		DPC-231		DPC-232		DPC-233		DPC-234		DPC-235		DPC-236		DPC-237		DPC-238		DPC-239		DPC-240		DPC-241		DPC-242		DPC-243		DPC-244		DPC-245		DPC-246		DPC-247		DPC-248		DPC-249		DPC-250		DPC-251		DPC-252		DPC-253		DPC-254		DPC-255		DPC-256		DPC-257		DPC-258		DPC-259		DPC-260		DPC-261		DPC-262		DPC-263		DPC-264		DPC-265		DPC-266		DPC-267		DPC-268		DPC-269		DPC-270		DPC-271		DPC-272		DPC-273		DPC-274		DPC-275		DPC-276		DPC-277		DPC-278		DPC-279		DPC-280		DPC-281		DPC-282		DPC-283		DPC-284		DPC-285		DPC-286		DPC-287		DPC-288		DPC-289		DPC-290		DPC-291		DPC-292		DPC-293		DPC-294		DPC-295		DPC-296		DPC-297		DPC-298		DPC-299		DPC-300		DPC-301		DPC-302		DPC-303		DPC-304		DPC-305		DPC-306		DPC-307		DPC-308		DPC-309		DPC-310		DPC-311		DPC-312		DPC-313		DPC-314		DPC-315		DPC-316		DPC-317		DPC-318		DPC-319		DPC-320		DPC-321		DPC-322		DPC-323		DPC-324		DPC-325		DPC-326		DPC-327		DPC-328		DPC-329		DPC-330		DPC-331		DPC-332		DPC-333		DPC-334		DPC-335		DPC-336		DPC-337		DPC-338		DPC-339		DPC-340		DPC-341		DPC-342		DPC-343		DPC-344		DPC-345		DPC-346		DPC-347		DPC-348		DPC-349		DPC-350		DPC-351		DPC-352		DPC-353		DPC-354		DPC-355		DPC-356		DPC-357		DPC-358		DPC-359		DPC-360		DPC-361		DPC-362		DPC-363		DPC-364		DPC-365		DPC-366		DPC-367		DPC-368		DPC-369		DPC-370		DPC-371		DPC-372		DPC-373		DPC-374		DPC-375		DPC-376		DPC-377		DPC-378		DPC-379		DPC-380		DPC-381		DPC-382		DPC-383		DPC-384		DPC-385		DPC-386		DPC-387		DPC-388		DPC-389		DPC-390		DPC-391		DPC-392		DPC-393		DPC-394		DPC-395		DPC-396		DPC-397		DPC-398		DPC-399		DPC-400		DPC-401		DPC-402		DPC-403		DPC-404		DPC-405		DPC-406		DPC-407		DPC-408		DPC-409		DPC-410		DPC-411		DPC-412		DPC-413		DPC-414		DPC-415		DPC-416		DPC-417		DPC-418		DPC-419		DPC-420		DPC-421		DPC-422		DPC-423		DPC-424		DPC-425		DPC-426		DPC-427		DPC-428		DPC-429		DPC-430		DPC-431		DPC-432		DPC-433		DPC-434		DPC-435		DPC-436		DPC-437		DPC-438		DPC-439		DPC-440		DPC-441		DPC-442		DPC-443		DPC-444		DPC-445		DPC-446		DPC-447		DPC-448		DPC-449		DPC-450		DPC-451		DPC-452		DPC-453		DPC-454		DPC-455		DPC-456		DPC-457		DPC-458		DPC-459		DPC-460		DPC-461		DPC-462		DPC-463		DPC-464		DPC-465		DPC-466		DPC-467		DPC-468		DPC-469		DPC-470		DPC-471		DPC-472		DPC-473		DPC-474		DPC-475		DPC-476		DPC-477		DPC-478		DPC-479		DPC-480		DPC-481		DPC-482		DPC-483		DPC-484		DPC-485		DPC-486		DPC-487		DPC-488		DPC-489		DPC-490		DPC-491		DPC-492		DPC-493		DPC-494		DPC-495		DPC-496		DPC-497		DPC-498		DPC-499		DPC-500		DPC-501		DPC-502		DPC-503		DPC-504		DPC-505		DPC-506		DPC-507		DPC-508		DPC-509		DPC-510		DPC-511		DPC-512		DPC-513		DPC-514		DPC-515		DPC-516		DPC-517		DPC-518		DPC-519		DPC-520		DPC-521		DPC-522		DPC-523		DPC-524		DPC-525		DPC-526		DPC-527		DPC-528		DPC-529		DPC-530		DPC-531		DPC-532		DPC-533		DPC-534		DPC-535		DPC-536		DPC-537		DPC-538		DPC-539		DPC-540		DPC-541		DPC-542		DPC-543		DPC-544		DPC-545		DPC-546		DPC-547		DPC-548		DPC-549		DPC-550		DPC-551		DPC-552		DPC-553		DPC-554		DPC-555		DPC-556		DPC-557		DPC-558		DPC-559		DPC-560		DPC-561		DPC-562		DPC-563		DPC-564		DPC-565		DPC-566		DPC-567		DPC-568		DPC-569		DPC-570		DPC-571		DPC-572		DPC-573		DPC-574		DPC-575		DPC-576		DPC-577		DPC-578		DPC-579		DPC-580		DPC-581		DPC-582		DPC-583		DPC-584		DPC-585		DPC-586		DPC-587		DPC-588		DPC-589		DPC-590		DPC-591		DPC-592		DPC-593		DPC-594		DPC-595		DPC-596		DPC-597		DPC-598		DPC-599		DPC-600		DPC-601		DPC-602		DPC-603		DPC-604		DPC-605		DPC-606		DPC-607		DPC-608		DPC-609		DPC-610		DPC-611		DPC-612		DPC-613		DPC-614		DPC-615		DPC-616		DPC-617		DPC-618		DPC-619		DPC-620		DPC-621		DPC-622		DPC-623		DPC-624		DPC-625		DPC-626		DPC-627		DPC-628		DPC-629		DPC-630		DPC-631		DPC-632		DPC-633		DPC-634		DPC-635		DPC-636		DPC-637		DPC-638		DPC-639		DPC-640		DPC-641		DPC-642		DPC-643		DPC-644		DPC-645		DPC-646		DPC-647		DPC-648		DPC-649		DPC-650		DPC-651		DPC-652		DPC-653		DPC-654		DPC-655		DPC-656		DPC-657		DPC-658		DPC-659		DPC-660		DPC-661		DPC-662		DPC-663		DPC-664		DPC-665		DPC-666		DPC-667		DPC-668		DPC-669		DPC-670		DPC-671		DPC-672		DPC-673		DPC-674		DPC-675		DPC-676		DPC-677		DPC-678		DPC-679		DPC-680		DPC-681		DPC-682		DPC-683		DPC-684		DPC-685		DPC-686		DPC-687		DPC-688		DPC-689		DPC-690		DPC-691		DPC-692		DPC-693		DPC-694		DPC-695		DPC-696		DPC-697		DPC-698		DPC-699		DPC-700		DPC-701		DPC-702		DPC-703		DPC-704		DPC-705		DPC-706		DPC-707		DPC-708		DPC-709		DPC-710		DPC-711		DPC-712		DPC-713		DPC-714		DPC-715		DPC-716		DPC-717		DPC-718		DPC-719		DPC-720		DPC-721		DPC-722		DPC-723		DPC-724		DPC-725		DPC-726		DPC-727		DPC-728		DPC-729		DPC-730		DPC-731		DPC-732		DPC-733		DPC-734		DPC-735		DPC-736		DPC-737		DPC-738		DPC-739		DPC-740		DPC-741		DPC-742		DPC-743		DPC-744		DPC-745		DPC-746		DPC-747		DPC-748		DPC-749		DPC-750		DPC-751		DPC-752		DPC-753		DPC-754		DPC-755		DPC-756		DPC-757		DPC-758		DPC-759		DPC-760		DPC-761		DPC-762		DPC-763		DPC-764		DPC-765		DPC-766		DPC-767		DPC-768		DPC-769		DPC-770		DPC-771		DPC-772		DPC-773		DPC-774		DPC-775		DPC-776		DPC-777		DPC-778		DPC-779		DPC-780		DPC-781		DPC-782		DPC-783		DPC-784		DPC-785		DPC-786		DPC-787		DPC-788		DPC-789		DPC-790		DPC-791		DPC-792		DPC-793		DPC-794		DPC-795		DPC-796		DPC-797		DPC-798		DPC-799		DPC-800		DPC-801		DPC-802		DPC-803		DPC-804		DPC-805		DPC-806		DPC-807		DPC-808		DPC-809		DPC-810		DPC-811		DPC-812		DPC-813		DPC-814		DPC-815		DPC-816		DPC-817		DPC-818		DPC-819		DPC-820		DPC-821		DPC-822		DPC-823		DPC-824		DPC-825		DPC-826		DPC-827		DPC-828		DPC-829		DPC-830		DPC-831		DPC-832		DPC-833		DPC-834		DPC-835		DPC-836		DPC-837		DPC-838		DPC-839		DPC-840		DPC-841		DPC-842		DPC-843		DPC-844		DPC-845		DPC-846		DPC-847		DPC-848		DPC-849		DPC-850		DPC-851		DPC-852		DPC-853		DPC-854		DPC-855		DPC-856		DPC-857		DPC-858		DPC-859		DPC-860		DPC-861		DPC-862		DPC-863		DPC-864		DPC-865		DPC-866		DPC-867		DPC-868		DPC-869		DPC-870		DPC-871		DPC-872		DPC-873		DPC-874		DPC-875		DPC-876		DPC-877		DPC-878		DPC-879		DPC-880		DPC-881		DPC-882		DPC-883		DPC-884		DPC-885		DPC-886		DPC-887		DPC-888		DPC-889		DPC-890		DPC-891		DPC-892	
-------	--	-------	--	-------	--	-------	--	-------	--	-------	--	-------	--	-------	--	-------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	--------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--	---------	--

3308

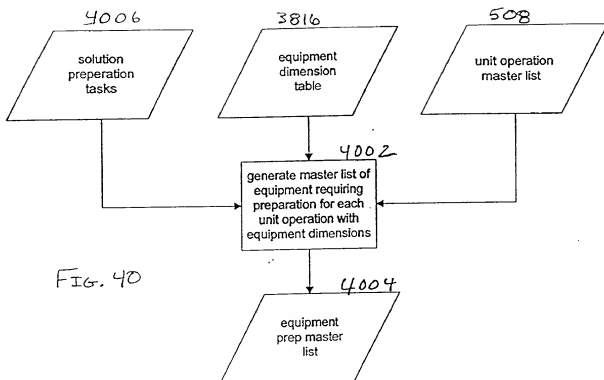


FIG. 40

3310

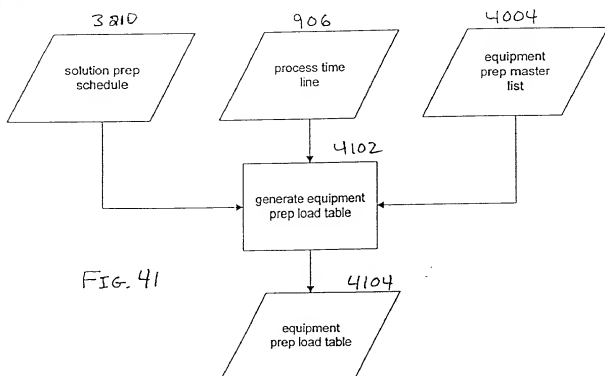


FIG. 41



4216

4214

4212

4210

Equipment Items	Unit Oper End Time DateTime						EPC-4			EPC-5			EPC-6					
			Flasks 0.25	Rubber Stoppers Silicone 0.00	Flexible Tubing Silicone 0.33	Total CF 3.33	Small Glassware Beakers 0.03125	Flasks 0.25	Total CF	PP Carboys			Total CF	BSG Carboys			Total CF	
										10L 1.3333	20L 4.88	45L 10.7		10L 1.3333	20L 4.88	45L 10.7		
1 Inoculum Prep	06/04/98	02:30 PM					0.00		6	1.25	1.25							0.00
2 Flask Growth	06/05/98	01:30 PM					0.00		5	1.25	1.25							0.00
3 Seed Fermentation	06/06/98	03:30 PM		4	4				4									0.00
4 Fermentation	06/07/98	12:00 PM		0.02	1.33		1.35	1.00	1									0.00
5 Heat Exchange	06/07/98	01:30 PM		4	4		1.35		0	5.33								0.00
6 Cont. Cent/Solids	06/07/98	11:51 AM					0.00		0									0.00
1 Inoculum Prep	06/06/98	02:30 PM					0.00		6	1.25	1.25							0.00
2 Flask Growth	06/07/98	01:30 PM					0.00		5	1.25	1.25							0.00
3 Seed Fermentation	06/08/98	03:30 PM					0.00		1.25									0.00
4 Fermentation	06/09/98	06:00 AM					0.00		0									0.00
5 Heat Exchange	06/09/98	10:00 AM					0.00		0									0.00
6 Cont. Cent/Solids	06/09/98	08:51 AM					0.00		0									0.00
1 Inoculum Prep	06/09/98	02:30 PM					0.00		5	1.25	1.25							0.00
2 Flask Growth	06/09/98	01:30 PM					0.00		6	1.25	1.25							0.00
3 Seed Fermentation	06/10/98	03:30 PM					0.00		1.25									0.00
4 Fermentation	06/03/98	10:00 AM					0.00		0									0.00
5 Heat Exchange	06/11/98	06:00 AM					0.00		0									0.00
6 Cont. Cent/Solids	06/11/98	08:51 AM					0.00		0									0.00
7 Cell Resuspension	06/11/98	12:16 PM					0.00		0									0.00
8 Heat Exchange	06/11/98	09:33 AM					0.00		0									0.00
9 Cell Disruption	06/11/98	09:51 AM					0.00		0									0.00
10 Heat Exchange	06/11/98	10:09 AM					0.00		6	1.25	1.25							0.00

FIG. 42B

Equipment Prep Load Table

4218 4220

Equipment Items	Unit Oper End Time Date	EPC-1		EPC-2		EPC-3				
		Specialty Glass Siphon Tubes	Total	Instruments DO Probe	Fittings pH Probe	Elbows	Crosses	Reducers	Hose Barb	Clamps
8 Heat Exchange	06/11/96 10:27 AM		0	0	0.06	0.03	0.02	0.08	0.01	0.01
8 Cell Disruption	06/11/96 10:45 AM		0	0						0.00
10 Heat Exchange	06/11/96 12:00 AM		0	0						0.00
8 Heat Exchange	06/11/96 02:21 PM		0	0						0.00
9 Cell Disruption	06/11/96 02:39 PM		0	0						0.00
10 Heat Exchange	06/11/96 02:57 PM		0	0						0.00
11 IB Reuspension	06/11/96 10:57 AM		0	0						0.00
12 Centrifugation	06/11/96 11:33 AM		0	0						0.00
11 IB Reuspension	06/11/96 03:08 PM		0	0						0.00
12 Centrifugation	06/11/96 03:12 PM		0	0						0.00
13 Renaturation	06/12/96 08:43 AM		0	0						0.00
14 Buffer Exchange	06/12/96 11:47 AM		0	0						0.00
15 Clarification	06/12/96 11:03 AM		0	0						0.00
16 Chromatography 1	06/12/96 03:39 PM		0	0						0.00
17 Chromatography 2	06/12/96 06:59 PM		0	0						0.00
18 Buffer Exchange	06/12/96 08:27 PM		0	0						0.00
19 Chromatography 3	06/12/96 10:07 PM		0	0						0.00
20 Buffer Exchange	06/12/96 10:38 PM		0	0						0.00
21 Chromatography 4	06/13/96 12:14 AM		0	0						0.00
22 Sterile Filtration	06/13/96 12:48 AM		0	0						0.00
Totals										3.25

FIG. 42C



42-22 Equipment Top Load Table

4226

4228

Equipment Items	Unit Oper End Time		EPC-4				EPC-5				EPC-6				
	Date	Time	Flasks 0.25	Rubber Stoppers Silicone 0.00	Flexible Tubing Silicone 0.33	Total CF 3.33	Small Glassware Beakers 0.03125	Flasks 0.25	Total CF 0.25	PP Carboys 10L 1.3333	20L 4.88	Total CF 10.7	BSG Carboys 10L 1.3333	20L 4.88	Total CF 10.7
8 Heat Exchange	06/11/06	10:27 AM				0.00			0			0.00			0.00
9 Cell Disruption	06/11/06	10:45 AM				0.00			0			0.00			0.00
10 Heat Exchange	06/11/06	12:00 AM				0.00		5	1.25	1.25		0.00			0.00
8 Heat Exchange	06/11/06	02:21 PM				0.00		1.25	1.25			0.00			0.00
9 Cell Disruption	06/11/06	02:59 PM				0.00			0			0.00			0.00
10 Heat Exchange	06/11/06	02:57 PM				0.00		5	1.25	1.25		0.00			0.00
11 IB Resuspension	06/11/06	10:57 AM				0.00			0			0.00			0.00
12 Centrifugation	06/11/06	11:33 AM				0.00			0			0.00			0.00
11 IB Resuspension	06/11/06	03:06 PM				0.00			0			0.00			0.00
12 Centrifugation	06/11/06	03:12 PM				0.00			0			0.00			0.00
13 Renaturation	06/12/06	05:43 AM				0.00			0			0.00			0.00
14 Buffer Exchange	06/12/06	11:47 AM				0.00			0			0.00			0.00
15 Clarification	06/12/06	11:03 AM				0.00			0			0.00			0.00
16 Chromatography 1	06/12/06	03:59 PM				0.00			0			0.00			0.00
17 Chromatography 2	06/12/06	05:59 PM				0.00			0			0.00			0.00
18 Buffer Exchange	06/12/06	08:27 PM				0.00			0			0.00			0.00
19 Chromatography 3	06/12/06	10:07 PM				0.00			0			0.00			0.00
20 Buffer Exchange	06/12/06	10:38 PM				0.00			0			0.00			0.00
21 Chromatography 4	06/13/06	12:14 AM				0.00			0			0.00			0.00
22 Sterile Filtration	06/13/06	12:48 AM				0.00			0			0.00			0.00
Totals									0						

FIG. 42D

3312

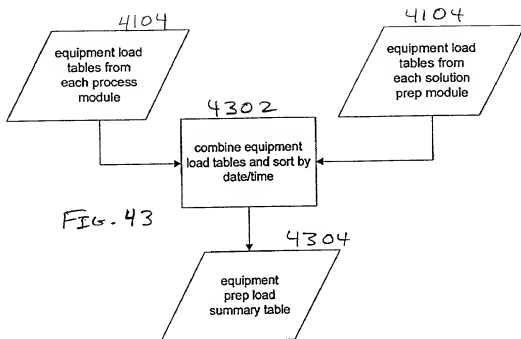


FIG. 43

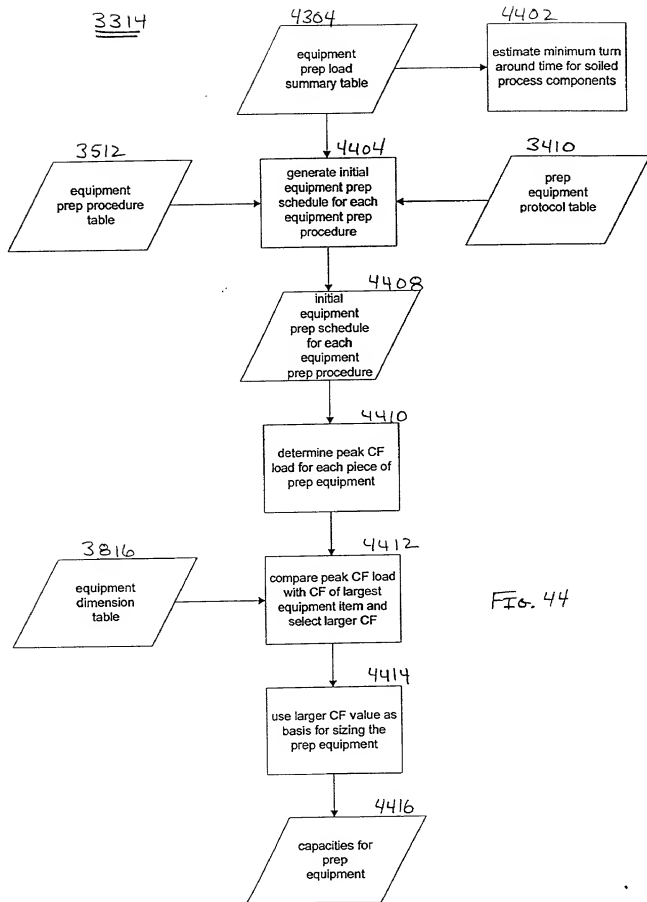


FIG. 44

4506

QC Load Table - PE Module

4504

4502

	Operation	QA/QC Samples										Chemical										Biological							Immunological		Act.					
		Start		Finish		Visual		AC-1		AC-2		AC-3		AC-4		AC-5		AB-1		AB-2		AB-3		AB-4		AB-5		AB-6		AB-7		AB-1		AB-2		
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AC-7	AC-8	AC-9	AC-10	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AB-8	AB-9	AB-10	AB-11	AB-12	AB-13		AB-14	AB-15	AB-16	AB-17	AB-18
1	1 A. Inoculum Prep	06/03/96	08:30 AM																																	
2	Set Up	06/03/96	09:30 AM	06/03/96	12:30 PM																															
3	Preincubation	06/03/96	12:30 PM	06/03/96	03:30 PM																															
4	Inoculation	06/03/96	03:30 PM	06/04/96	02:30 PM																															
5	Clean Up	06/04/96	02:30 PM	06/04/96	02:45 PM																															
6	Subtotal																																			
7																																				
8	2 A. Flask Growth																																			
9	Set Up	06/04/96	12:30 PM	06/04/96	01:30 PM																															
10	Preincubation	06/04/96	01:30 PM	06/04/96	02:30 PM																															
11	Inoculation	06/04/96	02:30 PM	06/05/96	01:30 PM																															
12	Clean Up	06/05/96	01:30 PM	06/05/96	01:45 PM																															
13	Subtotal																																			
14																																				
15	3 A. Seed Fermentation																																			
16	Set Up	06/05/96	11:30 AM	06/05/96	12:30 PM																															
17	Preincubation	06/05/96	12:30 PM	06/05/96	01:30 PM																															
18	Fermentation	06/05/96	01:30 PM	06/06/96	10:30 AM																															
19	Harvest	06/06/96	10:30 AM	06/06/96	11:00 AM																															
20	CIP	06/06/96	10:30 AM	06/06/96	11:30 AM																															
21	SIP	06/06/96	11:30 AM	06/06/96	12:30 PM																															
22	Clean Up	06/06/96	12:30 PM	06/06/96	03:30 PM																															
23	Subtotal																																			
24																																				
25	4 A. Production Fermentation																																			
26	Set Up	06/06/96	09:00 AM	06/06/96	10:00 AM																															
27	Preincubation	06/06/96	10:00 AM	06/06/96	11:00 AM																															
28	Fermentation	06/06/96	11:00 AM	06/07/96	08:00 AM																															
29	CIP	06/07/96	08:00 AM	06/07/96	09:00 AM																															
30	SIP	06/07/96	09:00 AM	06/07/96	10:00 AM																									</						

Fig. 45A

FIG. 45B

## QC Load Table - PE Module

Operation		QA/QC Samples																								
		Visual				Chemical						Biochemical						Immunological		Act.						
		AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2	AA-1							
Date	Time	Date	Time																							
95	SIP	06/03/96	05:30 AM	06/07/96	11:30 AM																					
96	Clean Up	06/07/96	10:00 AM	06/07/96	01:00 PM																					
97	Subtotal	06/07/96	11:30 AM	06/07/96	01:00 PM																					
98																										
99	6 B Cont. Cent./Solids																									
100	Set Up	06/07/96	06:00 AM	06/07/96	06:30 AM																					
101	Centrifugation	06/07/96	06:00 AM	06/07/96	06:30 AM																					
102	Wash	06/07/96	10:00 AM	06/07/96	10:30 AM																					
103	CIP	06/07/96	10:00 AM	06/07/96	10:21 AM																					
104	SIP	06/07/96	10:21 AM	06/07/96	11:21 AM																					
105	Clean Up	06/07/96	11:21 AM	06/07/96	11:51 AM																					
106	Sub Total	06/07/96	11:51 AM	06/07/96	11:51 AM																					
107																										
108																										
109	1 C Incubulum Prep																									
110	Set Up	06/03/96	01:30 PM	06/03/96	02:30 PM																					
111	Preincubation	06/03/96	02:30 PM	06/03/96	03:30 PM																					
112	Incubation	06/03/96	03:30 PM	06/03/96	04:30 PM																					
113	Clean Up	06/04/96	02:30 PM	06/04/96	02:45 PM																					
114	Subtotal	06/04/96	02:30 PM	06/04/96	02:45 PM																					
115																										
116	2 C Flask Growth																									
117	Set Up	06/04/96	12:30 PM	06/04/96	01:30 PM																					
118	Preincubation	06/04/96	01:30 PM	06/04/96	02:30 PM																					
119	Incubation	06/04/96	02:30 PM	06/04/96	03:30 PM																					
120	Clean Up	06/05/96	01:30 PM	06/05/96	01:45 PM																					
121	Subtotal	06/05/96	01:30 PM	06/05/96	01:45 PM																					
122																										
123	3 C Seed Fermentation																									
124	Set Up	06/05/96	11:30 AM	06/05/96	12:30 PM																					
125	Preincubation	06/05/96	12:30 PM	06/05/96	01:30 PM																					
126	Fermentation	06/05/96	01:30 PM	06/05/96	10:30 AM																					
127	Harvest	06/05/96	10:30 AM	06/05/96	11:30 AM																					
128	CIP	06/05/96	11:30 AM	06/05/96	12:30 PM																					
129	SIP	06/05/96	12:30 PM	06/05/96	03:30 PM																					
130	Clean Up	06/05/96	03:30 PM	06/05/96	03:30 PM																					
131	Subtotal	06/05/96	03:30 PM	06/05/96	03:30 PM																					
132																										
133	4 C Production Fermentation																									
134	Set Up	06/05/96	09:00 AM	06/05/96	10:00 AM																					
135	Preincubation	06/05/96	10:00 AM	06/05/96	11:00 AM																					
136	Fermentation	06/05/96	11:00 AM	06/07/96	09:00 AM																					
137	CIP	06/07/96	09:00 AM	06/07/96	10:00 AM																					
138	SIP	06/07/96	09:00 AM	06/07/96	10:00 AM																					
139	Clean Up	06/07/96	10:00 AM	06/07/96	12:30 PM																					
140																										
141																										

Fig. 45C

	Operation	QMAC Samples										Immunological					
		Start		Finish		Visual		Chemical		Biochemical		AB-1		AB-2		AB-3	
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AB-1	AB-2	AB-3	AB-4	AB-5
142	Subtotal	06/07/96	08:00 AM														
143	8 C Heat Exchange																
144	Set Up	06/07/96	08:00 AM	06/07/96	08:30 AM												
145	Transfer	06/07/96	08:00 AM	06/07/96	09:00 AM												
146	CIP	06/07/96	08:00 AM	06/07/96	10:00 AM												
147	SIP	06/07/96	10:00 AM	06/07/96	11:00 AM												
148	Subtotal	06/07/96	11:00 AM	06/07/96	01:00 PM												
149	8 C Cont. Cent. Solids																
150	Set Up	06/07/96	09:00 AM	06/07/96	09:00 AM												
151	Configuration	06/07/96	09:00 AM	06/07/96	10:00 AM												
152	Wash	06/07/96	10:00 AM	06/07/96	10:30 AM												
153	CIP	06/07/96	10:30 AM	06/07/96	11:00 AM												
154	SIP	06/07/96	11:00 AM	06/07/96	11:30 AM												
155	Subtotal	06/07/96	11:30 AM	06/07/96	12:00 PM												
156	7 A. Resububilization																
157	Set Up	06/07/96	09:30 AM	06/07/96	10:00 AM												
158	Dilution	06/07/96	10:00 AM	06/07/96	10:30 AM												
159	Agitate	06/07/96	10:30 AM	06/07/96	11:00 AM												
160	SIP	06/07/96	11:00 AM	06/07/96	11:30 AM												
161	Subtotal	06/07/96	11:30 AM	06/07/96	12:00 PM												
162	8 A. Heat Exchange																
163	Set Up	06/07/96	11:00 AM	06/07/96	11:30 AM												
164	Transfer	06/07/96	11:30 AM	06/07/96	11:54 AM												
165	CIP	06/07/96	11:54 AM	06/07/96	12:24 PM												
166	SIP	06/07/96	12:24 PM	06/07/96	12:54 PM												
167	Subtotal	06/07/96	12:54 PM	06/07/96	01:24 PM												
168	9 A. Homogenization																
169	Set Up	06/07/96	11:30 AM	06/07/96	11:54 AM												
170	Transfer	06/07/96	11:54 AM	06/07/96	12:24 PM												
171	CIP	06/07/96	12:24 PM	06/07/96	12:54 PM												
172	SIP	06/07/96	12:54 PM	06/07/96	01:24 PM												
173	Subtotal	06/07/96	01:24 PM	06/07/96	01:54 PM												
174	8 A. Heat Exchange																
175	Set Up	06/07/96	11:00 AM	06/07/96	11:30 AM												
176	Transfer	06/07/96	11:30 AM	06/07/96	11:54 AM												
177	CIP	06/07/96	11:54 AM	06/07/96	12:24 PM												
178	SIP	06/07/96	12:24 PM	06/07/96	12:54 PM												
179	Subtotal	06/07/96	12:54 PM	06/07/96	01:24 PM												
180	9 A. Homogenization																
181	Set Up	06/07/96	11:30 AM	06/07/96	11:54 AM												
182	Transfer	06/07/96	11:54 AM	06/07/96	12:24 PM												
183	CIP	06/07/96	12:24 PM	06/07/96	12:54 PM												
184	SIP	06/07/96	12:54 PM	06/07/96	01:24 PM												
185	Subtotal	06/07/96	01:24 PM	06/07/96	01:54 PM												
186	8 A. Heat Exchange																
187	Set Up	06/07/96	11:00 AM	06/07/96	11:30 AM												
188	Transfer	06/07/96	11:30 AM	06/07/96	11:54 AM												
189	CIP	06/07/96	11:54 AM	06/07/96	12:24 PM												
190	SIP	06/07/96	12:24 PM	06/07/96	12:54 PM												
191	Subtotal	06/07/96	12:54 PM	06/07/96	01:24 PM												

FIG. 4SD

## QC Load Table - PE Module

QC Load Table - PE Module  
 QC Load Table - PE Module  
 QC Load Table - PE Module

Operation	Start				Finish				QA/QC Samples										Immunological											
	Date	Time	Date	Time	Date	Time	Date	Time	Visual	Chemical	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	Biochemical	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AB-1	AB-2	AB-1	AB-2		
13 A Heat Exchange	06/07/96	08:00 AM																												
191 Set Up	06/07/96	12:04 PM	06/07/96	12:34 PM																										
192 Transfer	06/07/96	12:34 PM	06/07/96	12:52 PM																										
193 CIP	06/07/96	12:52 PM	06/07/96	12:52 PM																										
194 SIP	06/07/96	12:52 PM	06/07/96	12:52 PM																										
195 Clean Up	06/07/96	12:52 PM	06/07/96	12:52 PM																										
196 Subtotal																														
197																														
198																														
199																														
200 8 B Heat Exchange																														
201 Set Up	06/07/96	12:52 PM	06/07/96	12:52 PM																										
202 Transfer	06/07/96	12:52 PM	06/07/96	01:10 PM																										
203 CIP	06/07/96	01:10 PM	06/07/96	01:10 PM																										
204 SIP	06/07/96	01:10 PM	06/07/96	01:10 PM																										
205 Clean Up	06/07/96	01:10 PM	06/07/96	01:10 PM																										
206 Subtotal																														
207																														
208																														
209 9 B Homogenization																														
210 Set Up	06/07/96	01:10 PM	06/07/96	01:10 PM																										
211 Lysis	06/07/96	01:51 PM	06/07/96	01:51 PM																										
212 CIP	06/07/96	01:51 PM	06/07/96	01:51 PM																										
213 SIP	06/07/96	01:51 PM	06/07/96	01:51 PM																										
214 Clean Up	06/07/96	01:51 PM	06/07/96	01:51 PM																										
215 Sub Total																														
216																														
217 10 B Heat Exchange																														
218 Set Up	06/07/96	01:51 PM	06/07/96	01:51 PM																										
219 Transfer	06/07/96	01:51 PM	06/07/96	02:09 PM																										
220 CIP	06/07/96	02:09 PM	06/07/96	02:09 PM																										
221 SIP	06/07/96	02:09 PM	06/07/96	02:09 PM																										
222 Clean Up	06/07/96	02:09 PM	06/07/96	02:09 PM																										
223 Subtotal																														
224																														
225																														
226 8 C Heat Exchange																														
227 Set Up	06/07/96	02:09 PM	06/07/96	02:09 PM																										
228 Transfer	06/07/96	02:09 PM	06/07/96	02:27 PM																										
229 CIP	06/07/96	02:27 PM	06/07/96	03:27 PM																										
230 SIP	06/07/96	03:27 PM	06/07/96	04:27 PM																										
231 Clean Up	06/07/96	04:27 PM	06/07/96	05:27 PM																										
232 Subtotal																														
233																														
234																														
235 9 C Homogenization																														
236 Set Up	06/07/96	02:27 PM	06/07/96	02:27 PM																										
237 Lysis	06/07/96	02:27 PM	06/07/96	03:07 PM																										
238																														
239																														

FIG. 45E



QC Load Table - PE Module

QC Load Table - PE Module

Operation	QA/QC Samples																						
	Visual				Chemical								Biotechnical								Immunological		
	Start Date	Time	Finish Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2	AA-1	
CIP	06/07/96	03:00 AM	06/07/96	04:07 PM																			
SIP	06/07/96	04:07 PM	06/07/96	05:07 PM																			
Clean Up	06/07/96	05:07 PM	06/07/96	06:07 PM																			
Sub Total																							
244																							
10 C Heat Exchange																							
246	06/07/96	03:07 PM	06/07/96	03:07 PM																			
247	06/07/96	03:07 PM	06/07/96	03:25 PM																			
Transfer	06/07/96	03:25 PM	06/07/96	04:25 PM																			
CIP	06/07/96	04:25 PM	06/07/96	05:25 PM																			
SIP	06/07/96	05:25 PM	06/07/96	06:25 PM																			
Clean Up	06/07/96	06:25 PM	06/07/96	07:25 PM																			
Subtotal																							
252																							
11 A Resubilization																							
254	06/07/96	11:52 AM	06/07/96	12:52 PM																			
Set Up	06/07/96	12:52 PM	06/07/96	01:22 PM																			
Dilution	06/07/96	01:22 PM	06/07/96	01:52 PM																			
Agitate	06/07/96	01:52 PM	06/07/96	01:52 PM																			
CIP	06/07/96	01:52 PM	06/07/96	02:52 PM																			
SIP	06/07/96	02:52 PM	06/07/96	03:52 PM																			
Clean Up	06/07/96	03:52 PM	06/07/96	04:52 PM																			
Subtotal																							
262																							
12 A Cont. Cent. Solids																							
264	06/07/96	12:52 PM	06/07/96	01:52 PM																			
Set Up	06/07/96	01:52 PM	06/07/96	02:22 PM																			
Centrifugation	06/07/96	02:22 PM	06/07/96	02:28 PM																			
Wash	06/07/96	02:28 PM	06/07/96	02:28 PM																			
CIP	06/07/96	02:28 PM	06/07/96	02:28 PM																			
SIP	06/07/96	02:28 PM	06/07/96	02:28 PM																			
Clean Up	06/07/96	02:28 PM	06/07/96	02:28 PM																			
Sub Total																							
272																							
11 B Resubilization																							
274	06/07/96	02:28 PM	06/07/96	02:28 PM																			
Set Up	06/07/96	02:28 PM	06/07/96	02:58 PM																			
Dilution	06/07/96	02:58 PM	06/07/96	03:13 PM																			
Agitate	06/07/96	03:13 PM	06/07/96	04:13 PM																			
CIP	06/07/96	04:13 PM	06/07/96	05:13 PM																			
SIP	06/07/96	05:13 PM	06/07/96	06:13 PM																			
Clean Up	06/07/96	06:13 PM	06/07/96	06:13 PM																			
Subtotal																							
282																							
12 B Cont. Cent. Solids																							
284	06/07/96	02:13 PM	06/07/96	03:13 PM																			
Set Up	06/07/96	03:13 PM	06/07/96	03:43 PM																			
Centrifugation	06/07/96	03:43 PM	06/07/96	03:49 PM																			
Wash	06/07/96	03:49 PM	06/07/96	03:49 PM																			
CIP	06/07/96	03:49 PM	06/07/96	03:49 PM																			
SIP	06/07/96	03:49 PM	06/07/96	03:49 PM																			
Clean Up	06/07/96	03:49 PM	06/07/96	03:49 PM																			
Subtotal																							

Fig. 45F

[illegible]

Fig. 456

## QC Load Table - PE Module

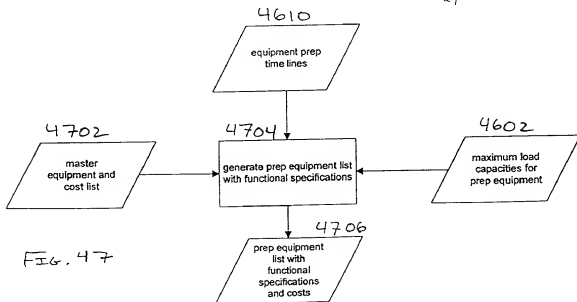
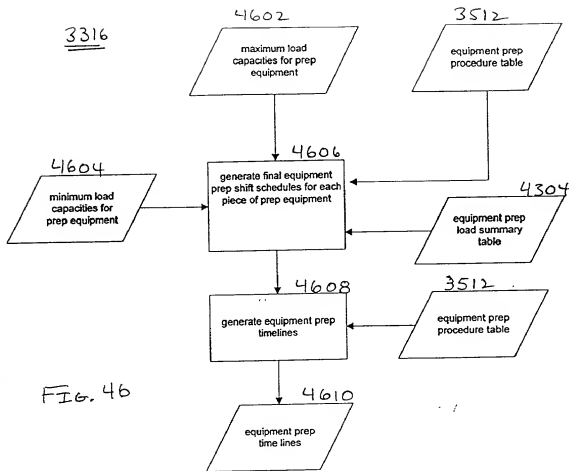
QC Load Table - PE Module  
 Date: 03/13/2013  
 Time: 03:13 PM  
 User: [Name]  
 Location: [Location]

	Operation	QA/QC Samples										Chemical										Biochemical										Immunological							
		Start		Finish		Visual		AC-1		AC-2		AC-3		AC-4		AC-5		AC-6		AB-1		AB-2		AB-3		AB-4		AB-5		AB-6		AB-7		AI-1		AI-2		AA-1	
		Date	Time	Date	Time	AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AC-6	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AB-8	AI-1	AI-2	AA-1															
338	Elute A	05/03/96	05:00 AM	05/03/96	05:12 PM																																		
339	Elute B	05/03/96	05:12 PM	05/03/96	05:25 PM																																		
340	Regenerate	05/03/96	05:25 PM	05/03/96	05:38 PM																																		
341	Store	05/03/96	05:38 PM	05/03/96	05:51 PM																																		
342	CIP	05/03/96	05:51 PM	05/03/96	06:04 PM																																		
343	SIP	05/03/96	06:04 PM	05/03/96	06:17 PM																																		
344	Clean Up	05/03/96	06:17 PM	05/03/96	06:30 PM																																		
345	Sub Total	05/03/96	06:30 PM	05/03/96	06:43 PM																																		
346																																							
347																																							
348	17 A TPA MPLC																																						
349	Equilibration	05/03/96	05:59 PM	05/03/96	06:12 PM																																		
350	Wash	05/03/96	06:12 PM	05/03/96	06:25 PM																																		
351	Elute A	05/03/96	06:25 PM	05/03/96	06:38 PM																																		
352	Elute B	05/03/96	06:38 PM	05/03/96	06:51 PM																																		
353	Regenerate	05/03/96	06:51 PM	05/03/96	07:04 PM																																		
354	Store	05/03/96	07:04 PM	05/03/96	07:17 PM																																		
355	CIP	05/03/96	07:17 PM	05/03/96	07:30 PM																																		
356	SIP	05/03/96	07:30 PM	05/03/96	07:43 PM																																		
357	Clean Up	05/03/96	07:43 PM	05/03/96	07:56 PM																																		
358	Sub Total	05/03/96	07:56 PM	05/03/96	08:13 PM																																		
359																																							
360																																							
361	18 A Flow Dialysis																																						
362	Set Up	05/03/96	03:29 PM	05/03/96	03:42 PM																																		
363	Flush	05/03/96	03:42 PM	05/03/96	03:55 PM																																		
364	Dialysis	05/03/96	03:55 PM	05/03/96	04:08 PM																																		
365	Wash	05/03/96	04:08 PM	05/03/96	04:21 PM																																		
366	Elute A	05/03/96	04:21 PM	05/03/96	04:34 PM																																		
367	Elute B	05/03/96	04:34 PM	05/03/96	04:47 PM																																		
368	Regenerate	05/03/96	04:47 PM	05/03/96	05:00 PM																																		
369	Store	05/03/96	05:00 PM	05/03/96	05:13 PM																																		
370	CIP	05/03/96	05:13 PM	05/03/96	05:26 PM																																		
371	SIP	05/03/96	05:26 PM	05/03/96	05:39 PM																																		
372	Clean Up	05/03/96	05:39 PM	05/03/96	05:52 PM																																		
373	Sub Total	05/03/96	05:52 PM	05/03/96	06:05 PM																																		
374																																							
375	19 A TPA MPLC																																						
376	Equilibration	05/03/96	05:59 PM	05/03/96	06:12 PM																																		
377	Wash	05/03/96	06:12 PM	05/03/96	06:25 PM																																		
378	Elute A	05/03/96	06:25 PM	05/03/96	06:38 PM																																		
379	Elute B	05/03/96	06:38 PM	05/03/96	06:51 PM																																		
380	Regenerate	05/03/96	06:51 PM	05/03/96	07:04 PM																																		
381	Store	05/03/96	07:04 PM	05/03/96	07:17 PM																																		
382	CIP	05/03/96	07:17 PM	05/03/96	07:30 PM																																		
383	SIP	05/03/96	07:30 PM	05/03/96	07:43 PM																																		
384	Clean Up	05/03/96	07:43 PM	05/03/96	07:56 PM																																		
385	Sub Total	05/03/96	07:56 PM	05/03/96	08:13 PM																																		

FIG. 45H

	Operation	QA/QC Samples										Immunological											
		Start		Finish		Visual	Chemical					Biochemical					Immunological						
		Date	Time	Date	Time		AV-1	AV-2	AC-1	AC-2	AC-3	AC-4	AC-5	AB-1	AB-2	AB-3	AB-4	AB-5	AB-6	AB-7	AI-1	AI-2	Act.
387	Clean Up	06/09/96	08:00 AM																				
388	Sub Total	06/09/96	10:39 AM	06/09/96	11:39 AM																		
389																							
390	20 A Flow Dialysis																						
391	Set Up	06/09/96	07:00 PM	06/09/96	07:00 PM																		
392	Flush	06/09/96	07:00 PM	06/09/96	07:40 PM																		
393	Prime	06/09/96	07:40 PM	06/09/96	08:20 PM																		
394	Dialysis	06/09/96	08:20 PM	06/09/96	09:00 PM																		
395	Wash	06/09/96	09:00 PM	06/09/96	09:40 PM																		
396	Flush	06/09/96	09:40 PM	06/09/96	10:20 PM																		
397	Wash	06/09/96	10:20 PM	06/09/96	11:00 PM																		
398	Prime	06/09/96	11:00 PM	06/09/96	11:20 PM																		
399	CIP	06/09/96	11:20 PM	06/09/96	11:20 PM																		
400	SIP	06/09/96	11:20 PM	06/09/96	12:20 AM																		
401	Clean Up	06/09/96	11:20 PM	06/09/96	12:20 AM																		
402	Sub Total	06/09/96	11:20 PM	06/09/96	12:20 AM																		
403	21 A PIA MPLC																						
404	Equilibration	06/09/96	09:28 PM	06/09/96	09:57 PM																		
405	Load	06/09/96	10:20 PM	06/09/96	10:28 PM																		
406	Wash	06/09/96	10:28 PM	06/09/96	11:01 PM																		
407	Elute A	06/09/96	11:01 PM	06/09/96	11:38 PM																		
408	Elute B	06/09/96	11:38 PM	06/09/96	11:38 PM																		
409	Regenerate	06/09/96	11:38 PM	06/09/96	11:42 PM																		
410	Store	06/09/96	11:42 PM	06/09/96	11:54 PM																		
411	CIP	06/09/96	11:54 PM	06/09/96	11:54 PM																		
412	SIP	06/09/96	11:54 PM	06/09/96	12:54 AM																		
413	Clean Up	06/09/96	11:54 PM	06/09/96	12:54 AM																		
414	Sub Total	06/09/96	11:54 PM	06/09/96	12:54 AM																		
415																							
416	22 A Sterile Filtration																						
417	Set Up	06/09/96	08:38 AM	06/09/96	08:38 AM																		
418	Filtration	06/09/96	11:38 PM	06/09/96	12:05 AM																		
419	Wash	06/09/96	12:05 AM	06/09/96	12:36 AM																		
420	Prime	06/09/96	12:36 AM	06/09/96	12:36 AM																		
421	CIP	06/09/96	12:36 AM	06/09/96	12:36 AM																		
422	Sub Total	06/09/96	12:36 AM	06/09/96	12:36 AM																		
423																							
424																							
425																							
426																							
427																							
428																							

Fig. 45I



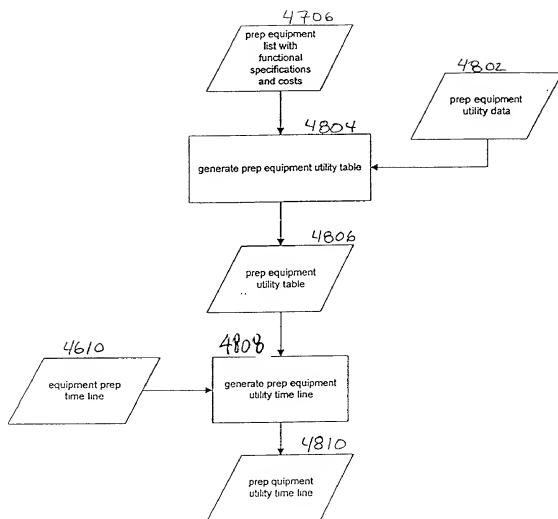
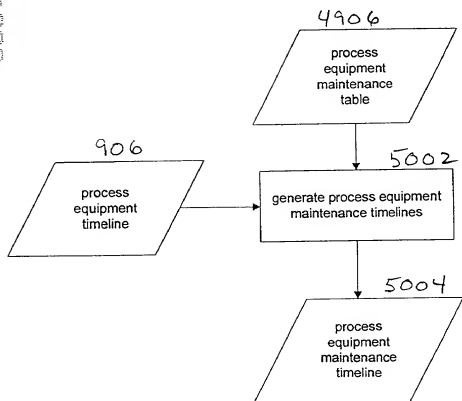
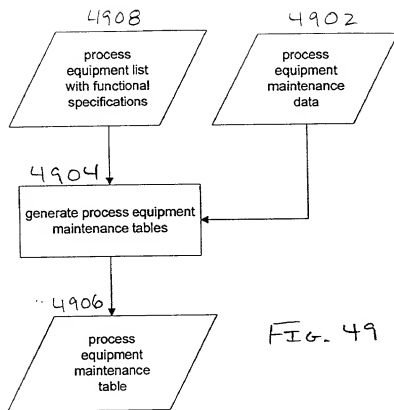
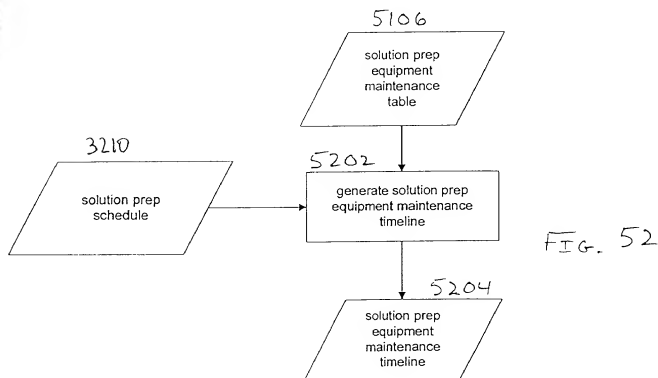
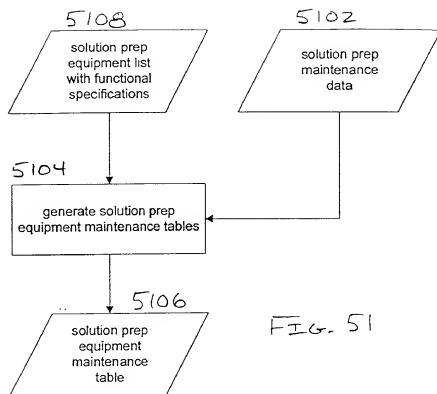
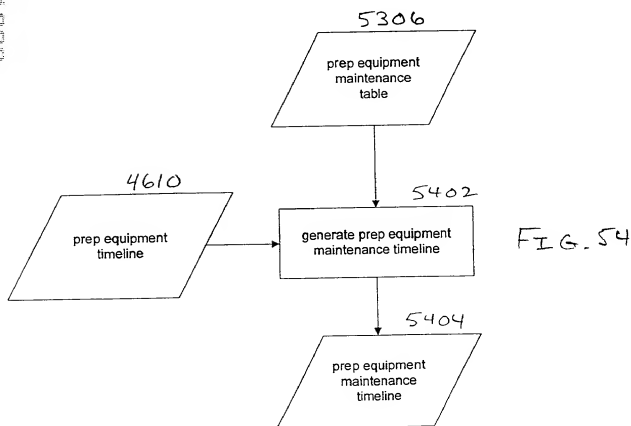
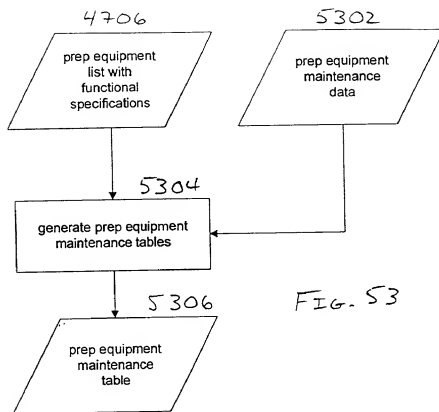


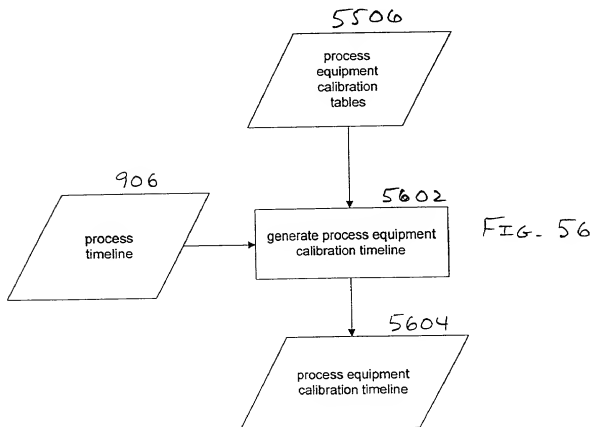
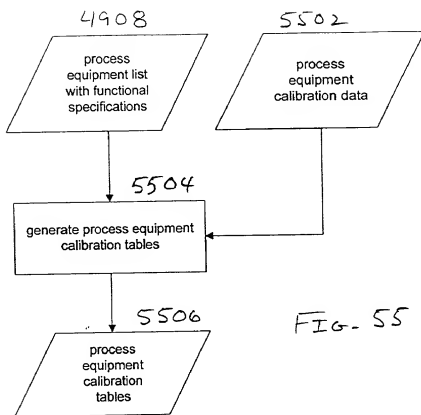
FIG. 48











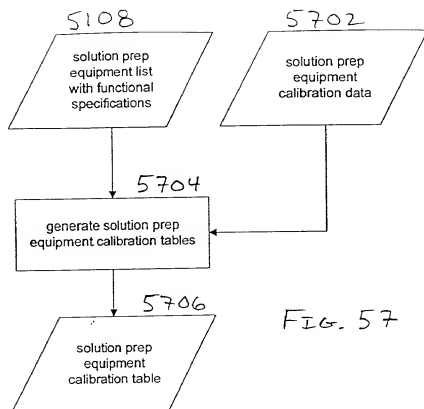


FIG. 57

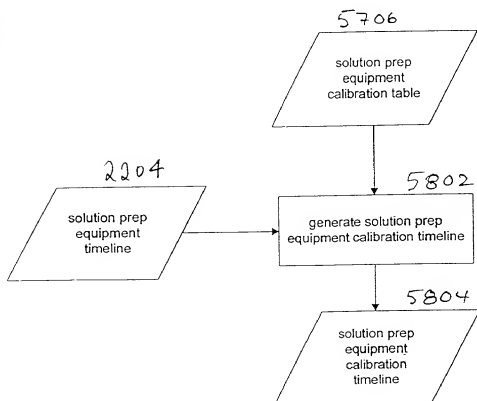
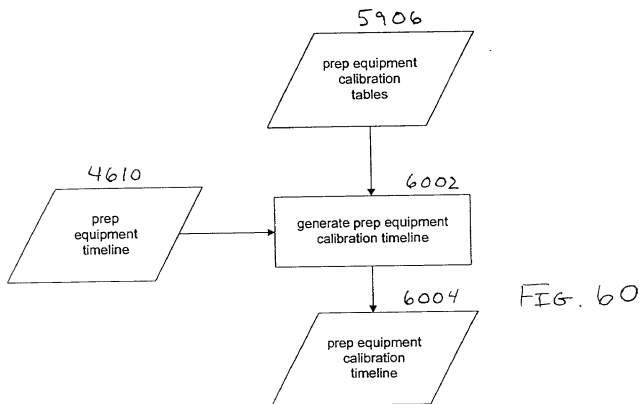
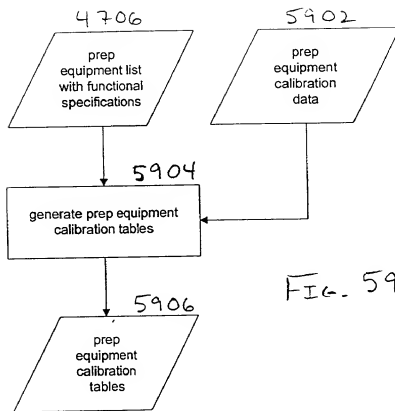


FIG. 58



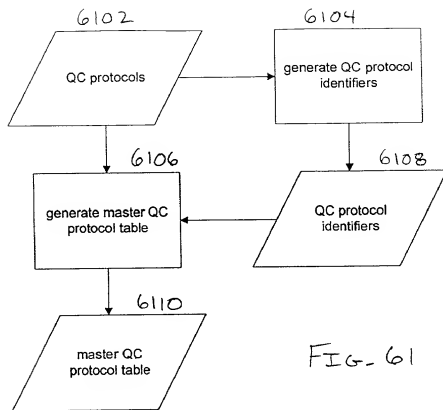


FIG. 61

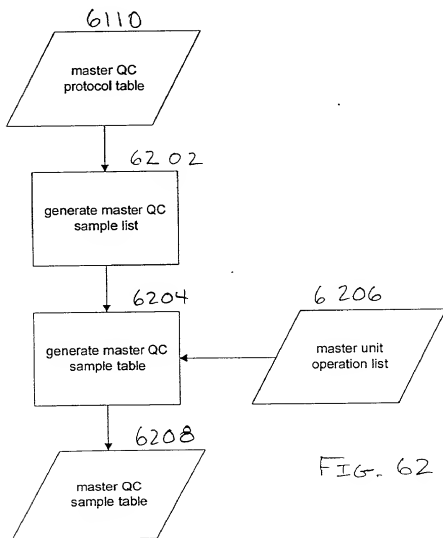


FIG. 62

Equipment Maintenance Table - Microbial Fermentation

6408

6406

6404

6402

Equipment Items	Filters						Gaskets						Bearings					
	Materials			Labor			Materials			Labor			Materials			Labor		
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
Incubator																		
-80 C Stock Freezer																		
Shaking Water Bath																		
Refrigerator																		
Floor Incubator-Shaker																		
Microscope																		
Seed Bioreactor																		
Production Bioreactor	45868	1	100	55	.55	.5	48094	1	500	55	.11	1					.035	
Harvest Heat Exchanger							62589	1	350	85	.249	1					.05	
Harvest Vessel																		
Agitator																		
Pump																		
Filter Holder																		
Manifolding																		
Instrumentation																		
MF Flush Vessel																		
MF Prime Vessel																		
MF Filtrate Vessel																		
Agitator																		
MF Wash Vessel																		
MF Regeneration Vessel																		
MF Storage Vessel																		

FIG. 64A

# Equipment Maintenance Table - Microbial Fermentation

6408 6410 6412

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
40 C Stock Freezer												
Shaking Water Bath												
Microscope												
Floor Incubator-Shaker												
Seed Boreador												
Production Boreador												
Harvest Heat Exchanger												
Harvest Vessel												
Agitator												
Pump												
Filler Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
Agitator												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												

Fig. 643

# Equipment Maintenance Table - Microbial Fermentation

6414

6416

6418

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
-80 C Stock Freezer												
Shaking Water Bath												
2 Liter Gas Wash Bottle												
Floor Incubator-Shaker												
Microscope												
Seed Bioreactor												
Production Bioreactor	500	25	.05	1	.035						78454	.5
Harvest Heat Exchanger												
Harvest Vessel												
Agiator												
Pump												
Filler Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
Agiator												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												

Fig. 64C



Equipment Maintenance Table - Microbial Fermentation

6418

6420

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Unit Cost
40 C Stock Freezer						
Shaking Water Bath						
220V 60Hz Floor Incubator-Shaker						
Microscope						
Seed Bioreactor	1.5	.03	.5			
Fermentation Production Bioreactor				56158	5	500
Harvest Heat Exchanger						
Harvest Vessel						
Agitator						
Pump						
Filter Holder						
Manifolding						
Instrumentation						
MF Flush Vessel						
MF Prime Vessel						
MF Filtrate Vessel						
Agitator						
MF Wash Vessel						
MF Regeneration Vessel						
MF Storage Vessel						

Fig. 64D

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings					
	Materials			Labor			Materials			Labor			Materials			Labor		
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
MF Wash Vessel																		
Pump																		
Filler Holder																		
Manifolding																		
Instrumentation																		
MF Flush Vessel																		
MF Prime Vessel																		
MF Filtrate Vessel																		
MF Wash Vessel																		
MF Regeneration Vessel																		
MF Storage Vessel																		
Resuspension Vessel																		
Stir Plate																		
Cell Disruptor																		
Lysate Vessel																		
Resuspension Vessel																		
Stir Plate																		
MF Wash Vessel																		
Pump																		
Filter Holder																		

FIG. 64E

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												
Resuspension Vessel												
Stir Plate												
Cell Disruptor												
Lysate Vessel												
Resuspension Vessel												
Stir Plate												
MF Wash Vessel												
Pump												
Filter Holder												

Fig. 64F

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
MF Cell Concentration												
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												
MF Cell Resuspension Vessel												
Reuspension Vessel												
Stir Plate												
Cell Disruptor												
Lysate Vessel												
MF Cell Concentration												
Reuspension Vessel												
Stir Plate												
MF Wash Vessel												
Pump												
Filter Holder												

Fig. 64G

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
MF Concentration Vessel						
MF Wash Vessel						
Pump						
Filter Holder						
Manifolding						
Instrumentation						
MF Flush Vessel						
MF Prime Vessel						
MF Filtrate Vessel						
MF Wash Vessel						
MF Regeneration Vessel						
MF Storage Vessel						
Resuspension Vessel						
Stir Plate						
Cell Disruptor						
Lysate Vessel						
Resuspension Vessel						
Stir Plate						
MF Wash Vessel						
Pump						
Filter Holder						

FIG. 604

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters					Gaskets					Bearings				
	Materials					Labor					Materials				
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Unit Cost	Cycle Life	Qty	Item No.	Hours	\$/Cycle	Item No.	
Manifolding Instrumentation															
MF Flush Vessel															
MF Prime Vessel															
MF Filtrate Vessel															
MF Dilute Vessel															
MF Wash Vessel															
MF Regeneration Vessel															
MF Storage Vessel															
Renaturation Vessel															
Renaturation Vessel															
Slit Plate															
Pump															
Filter Holder															
Manifolding Instrumentation															
UF Flush Vessel															
UF Prime Vessel															
UF Filtrate Vessel															
UF Wash Vessel															
UF Diluent Vessel															
UF Regeneration Vessel															
UF Storage Vessel															

FIG. 64I

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts							
	Labor			Materials			Labor			Materials				
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty
Manifolding Instrumentation														
MF Flush Vessel														
MF Prime Vessel														
MF Filtrate Vessel														
MF Dilute Vessel														
MF Wash Vessel														
MF Regeneration Vessel														
MF Storage Vessel														
Renaturant Vessel														
Stir Plate														
Pump														
Filter Holder														
Manifolding Instrumentation														
UF Flush Vessel														
UF Prime Vessel														
UF Filtrate Vessel														
UF Wash Vessel														
UF Diluent Vessel														
UF Regeneration Vessel														
UF Storage Vessel														

FIG-64J

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shifts						Lubricant					
	Labor			Materials			Labor			Materials		
	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life
Manifolding Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Dilute Vessel												
MF Wash Vessel												
MF Regeneration Vessel												
MF Storage Vessel												
Renatrant Vessel												
Stir Plate												
Pump												
Filter Holder												
Manifolding Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												

FIG. 64 K





Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Fillers						Gaskets						Bearings					
	Materials Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Labor Hours	Materials Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Labor Hours	Materials Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Labor Hours
UF Waste Vessel																		
Chromatography Column																		
Pump																		
Inst. & Control System																		
Manifolding																		
Equilibration Vessel																		
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		
Storage Vessel																		
Waste Vessel (1)																		
Product Vessel																		
Waste Vessel (2)																		
Chromatography Column																		
Pump																		
Inst. & Control System																		
Manifolding																		
Equilibration Vessel																		
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		

FIG- 64h

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts						
	Labor			Materials			Labor			Materials			
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty
UF Waste Vessel													
Chromatography Column													
Pump													
Inst. & Control System													
Manifolding													
Equilibration Vessel													
Wash Vessel													
Eluent Vessel													
Regenerate Vessel													
Storage Vessel													
Waste Vessel (1)													
Product Vessel													
Waste Vessel (2)													
Chromatography Column													
Pump													
Inst. & Control System													
Manifolding													
Equilibration Vessel													
Wash Vessel													
Eluent Vessel													
Regenerate Vessel													

FIG. 6 UN

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shafts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
UF Waste Vessel												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												

FIG. 640

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
UF Waste Vessel						
Chromatography Column						
Pump						
Inst. & Control System						
Manifolding						
Equilibration Vessel						
Wash Vessel						
Eluent Vessel						
Regenerate Vessel						
Storage Vessel						
Waste Vessel (1)						
Product Vessel						
Waste Vessel (2)						
Chromatography Column						
Pump						
Inst. & Control System						
Manifolding						
Equilibration Vessel						
Wash Vessel						
Eluent Vessel						
Regenerate Vessel						

Fig. 6JP



Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
	Labor			Materials			Labor			Materials		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	\$/Cycle	Hours	\$/Cycle	Item No.	Qty
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Buffer/Exchange Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												

Fig. 642

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shifts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
Buffer/Exchange Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
Chromatography Column												
Pump												
Inst. & Control System												
Manifolding												
Equilibration Vessel												

Fig. 64



Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life
Storage Vessel						
Waste Vessel (1)						
Product Vessel						
Waste Vessel (2)						
Pump						
Filter Holder						
Manifolding						
Instrumentation						
UF Flush Vessel						
UF Prime Vessel						
UF Filtrate Vessel						
UF Wash Vessel						
UF Diluent Vessel						
UF Regeneration Vessel						
UF Storage Vessel						
UF Waste Vessel						
Chromatography Column						
Pump						
Inst. & Control System						
Manifolding						
Equilibration Vessel						

FIG- 64T

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters						Gaskets						Bearings					
	Materials			Labor			Materials			Labor			Materials					
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		
Storage Vessel																		
Waste Vessel (1)																		
Product Vessel																		
Waste Vessel (2)																		
200L Buffer exchange																		
Pump																		
Filter Holder																		
Manifolding																		
Instrumentation																		
UF Flush Vessel																		
UF Prime Vessel																		
UF Filtrate Vessel																		
UF Wash Vessel																		
UF Diluent Vessel																		
UF Regeneration Vessel																		
UF Storage Vessel																		
UF Waste Vessel																		
200L Chromatography																		
Chromatography Column																		
Pump																		

FIG. 64U

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts						
	Labor			Materials			Labor			Materials			
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Cycle Life	Unit Cost	\$/Cycle	Hours	Item No.	Qty
Wash Vessel													
Eluent Vessel													
Regenerate Vessel													
Storage Vessel													
Waste Vessel (1)													
Product Vessel													
Waste Vessel (2)													
20 Liter Exchange Vessel													
Pump													
Filter Holder													
Manifolding													
Instrumentation													
UF Flush Vessel													
UF Prime Vessel													
UF Filtrate Vessel													
UF Wash Vessel													
UF Diluent Vessel													
UF Regeneration Vessel													
UF Storage Vessel													
UF Waste Vessel													
20 Liter Chromatography Vessel													
Chromatography Column													
Pump													

FIG. 64V

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shifts						Lubricant					
	Labor			Materials			Labor			Materials		
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
205 BioProcess Changeover												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
UF Flush Vessel												
UF Prime Vessel												
UF Filtrate Vessel												
UF Wash Vessel												
UF Diluent Vessel												
UF Regeneration Vessel												
UF Storage Vessel												
UF Waste Vessel												
210 Chromatography												
Chromatography Column												
Pump												

FIG. 64W

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media					
	Labor			Materials		
	Unit Cost	\$/Cycle	Hours	Item No.	Qty	Cycle Life
	Unit Cost	\$/Cycle	Hours	Unit Cost	\$/Cycle	Hours
Wash Vessel						
Eluent Vessel						
Regenerate Vessel						
Storage Vessel						
Waste Vessel (1)						
Product Vessel						
Waste Vessel (2)						
200 Liter Exchange Vessel						
Pump						
Filter Holder						
Manifolding						
Instrumentation						
UF Flush Vessel						
UF Prime Vessel						
UF Filtrate Vessel						
UF Wash Vessel						
UF Diluent Vessel						
UF Regeneration Vessel						
UF Storage Vessel						
UF Waste Vessel						
200 Liter Chromatography Vessel						
Chromatography Column						
Pump						

FIG. 64X

# Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Filters				Gaskets				Bearings			
	Materials		Labor		Materials		Labor		Materials		Labor	
	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Hours	\$/Cycle	Hours	\$/Cycle	Item No.
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												

Equipment Maintenance Table - Microbial Fermentation

FIG. 64Y

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Seals						Belts					
				Labor			Materials			Labor		
	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours
Inst. & Control System												
Manifolding												
Equilibration Vessel												
Wash Vessel												
Eluent Vessel												
Regenerate Vessel												
Storage Vessel												
Waste Vessel (1)												
Product Vessel												
Waste Vessel (2)												
225 Surface (Catalytic) Wash Vessel												
MF Wash Vessel												
Pump												
Filter Holder												
Manifolding												
Instrumentation												
MF Flush Vessel												
MF Prime Vessel												
MF Filtrate Vessel												
MF Wash Vessel												

Fig. 642

Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Shirts														Lubricant			
	Labor						Materials		Labor						Materials			
	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life			
Inst. & Control System																		
Manifolding																		
Equilibration Vessel																		
Wash Vessel																		
Eluent Vessel																		
Regenerate Vessel																		
Storage Vessel																		
Waste Vessel (1)																		
Product Vessel																		
Waste Vessel (2)																		
22.8.2																		



Equipment Maintenance Table - Microbial Fermentation

Equipment Items	Thermal Media										
					Materials			Labor			
	Unit Cost	\$/Cycle	Hours	\$/Cycle	Item No.	Qty	Cycle Life	Unit Cost	\$/Cycle	Hours	\$/Cycle
Inst. & Control System											
Manifolding											
Equilibration Vessel											
Wash Vessel											
Eluent Vessel											
Regenerate Vessel											
Storage Vessel											
Waste Vessel (1)											
Product Vessel											
Waste Vessel (2)											
22-G Sterile Filtration											
MF Wash Vessel											
Pump											
Filter Holder											
Manifolding											
Instrumentation											
MF Flush Vessel											
MF Prime Vessel											
MF Filtrate Vessel											
MF Wash Vessel											

A1



Master Process Parameter Table - Biopharmaceutical

Unit Operation Type	Group 1		Group 2		Group 3	
	Parameter	Setp.	Parameter	Setp.	Parameter	Setp.
121 Product Fill by Solids	Reagent Concentration	1 M	Agitate Reagent/Lane Product Temperature Additional Mix Time	0.25 L/L 4 C 0.5 Hours 2 Hours	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
122 Product Fill by Liquids	Reagent Concentration	1 M	Lane Reagent/Lane Product Temperature Additional Mix Time	0.25 L/L 0.5 Hours 0.5 Hours 2 Hours	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
123 Concentration Fill by Solids	Reagent Concentration	1 M	Agitate Reagent/Lane Product Temperature Additional Mix Time	0.25 L/L 0.5 Hours 0.5 Hours 2 Hours	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
124 Concentration Fill by Liquids	Reagent Concentration	1 M	Lane Reagent/Lane Product Temperature Additional Mix Time	0.25 L/L 0.5 Hours 0.5 Hours 2 Hours	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
125 Spent Harvest Reagent Flow up	Priority Flow Rate Average Flow Rate 40 Pigs at 10 C Flow Throughput 400 g/gDP Flowback Time	20 Liters 11 L/SPH at 40 Pigs at 10 C 1 HR	Flowback Concentration Factor Flowback Flowback Flowback	2 LSF 2 LSF 10 Fold 0.5 C 1 LSF 2 LSF	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
126 Condensate Concentration Solvent Removal	System Void Volume	5 Liters	RCF Time Volume Reduction Wash Volume	10,000 X.O 60 Minutes 15 X/Vol. Reduction 0.2 X System Void Volume	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
127 Condensate Concentration Supplement Harvest	System Void Volume	6 Liters	RCF Time Volume Reduction Wash Volume	10,000 X.O 30 Minutes 15 X/Vol. Reduction 1.5 X System Void Volume	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
128 Dewater	System Void Volume	6 Liters	RCF Time Volume Reduction Wash Volume	10,000 X.O 30 Minutes 15 X/Vol. Reduction 1.5 X System Void Volume	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	65% 65% Y Y Y
129 Batch Concentration Solid Harvest	System Void Volume	6 Liters	RCF Time Volume Reduction Wash Volume	10,000 X.O 30 Minutes 15 X/Vol. Reduction 1.5 X System Void Volume	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP	65% 65% Y Y

A3

Master Process Parameters Table - Biopharmaceutical

Unit Operation Type	Group 1		Group 2		Group 3	
	Parameter	Spin	Parameter	Boil	Parameter	Spin
132 Batch Sterilization Syringe/HVLP	System and volume		10000 X 0.05 L 15 X HVLP Reduction 1.5 X System Vial Volume		SP	Y
		5 Liters	10000 X 0.05 L 15 X HVLP Reduction 1.5 X System Vial Volume		SP	95% 95%
133 Cell Division High Press Homogen	Product Attributes Vial Volume	6 C 5 Liters	Number of Passes Flow Rate Temperature Increase		Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		6 C 5 Liters	10,000 5 LPM 1.8 Degrees C (1000 PSI)		SP	600% Vial Volumes 95% 95%
134 Cell Division Bead Mill	Number of Passes Bead Size Flow Rate	2 0.5 LPM			Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		2			SP	95%
135 Cell Division Chemical Lysis	Reagent Exposure Time	0.5 M NaOH 4 C 2 Hours	Drug Suspension Product Tension	0.4 GPa 0 Molar	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		0.5 M NaOH 4 C 2 Hours			SP	95%
136 Concentration Tangential Flow	Product Average Flow Rate Total Throughput Filtration Time	1.5 Microns 50 L/Min at 40 Psi at 400 LinesSF 2.0 HR	Flux Prime Wash Solids Regenerate Store	2.00 USF 2.00 USF 0.30% Of Product Solution 1.00 USF 2.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		1.5 Microns 50 L/Min at 40 Psi at 400 LinesSF 2.0 HR			SP	95%
137 Concentration Dead End	Product Average Flow Rate Filtration Time	0.2 Microns 50 L/Min at 4 C 400 LinesSF 2.5 HR	Flux Prime Wash Solids Regenerate Store	0 USF 0.5 USF 0.03% Of Product Solution 1 USF 2 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		0.2 Microns 50 L/Min at 4 C 400 LinesSF 2.5 HR			SP	95%
138 Concentration Concentration/Clutch	Product Average Flow Rate Concentration Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
139 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
140 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
141 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
142 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
143 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
144 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
145 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
146 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
147 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
148 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
149 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%
150 Concentration Flow Dialysis	Product Average Flow Rate Dialysis Time	60 K MMAL 2 L/Min at 4 C 2 HR	Flux Prime Wash Solids Regenerate	2.00 USF 0.00 USF 10.0 Fold 0.50% Of Product Solution 1.00 USF	Step Recovery of Product Step Recovery of T.P. Temperature Regulation CIP SP	Y Y Y Y Y
		60 K MMAL 2 L/Min at 4 C 2 HR			SP	95% USF 95%

A4

45

Master Process Parameters Table - Biopharmaceutical

Unit Operation Type	Group 1		Group 2		Group 3	
	Parameter	Set	Parameter	Set	Parameter	Set
149 Enzymatic Hydrolysis	Enzyme to Product Ratio Reaction Temperature Reaction Time Reaction Duration	0.04 L/units of Enzyme Stock per 100g of Product 2 Night 37 Degree C 30 Minutes 100%	Transition Solution -1 Transition Solution -2 Neutralization		Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
152 Lyophilisation	Product Concentration Product Unit Size	8 Units 100 Grams/Unit	Lyophilization Time Product Weight Reduction	18 Hours 9.5%	Stop Recovery of Product Stop Recovery of T.P. CIP SIP	95% 95% Y Y Y
151 Heat Exchange	Process Inlet Temp Process Final Temp Utility Inlet Temp Utility Final Temp Process Inlet Temp Design Type (P1-C)	65.2 Degree C 35.2 Degree C 34 Degree C 34 Degree C 34.5 Degree C P	Exposure Time	1 Hour	Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation SIP	100% 100% Y Y Y
152 Storage					Stop Recovery of Product Stop Recovery of T.P. Temperature Regulation CIP SIP	95% 95% Y Y Y
153 Fermentation	Scale Up Ratio Fermenter Working Volume Fermenter Aeration Biomass Aseptic	10 Fold 50 Liters 100% 1 M/L 5 M/L 5 M/L	Growth Temperature Agitation Aeration Biomass Total Duration	37 Hours 1 RPM/100L 1 RPM/100L 5 RPM/100L 21 Hrs	Final OD CIP SIP	12 Y Y
144 Inlet Sealing	Final Feed Volume Spray Spill Ratio Number of PBS Washes Number of Media Washes No. of Media Washes	12 Liters 4 Containers 2 Containers 2 PBS 2 PBS	Serum Content Feed Rate Days in Confluence	2% FBS Feed per vessel per 2 Days 2 Days	Amplification Factor	1
151 Culture Media Syst	Final Feed Volume Spray Spill Ratio Number of PBS Washes Number of Media Washes No. of Media Washes	12 Liters 4 Containers 2 Containers 2 PBS 2 PBS	Serum Content Feed Rate Days in Confluence	2% FBS Feed per vessel per 2 Days 2 Days	Amplification Factor	1
146 Culture Flask Syst						
147 Control Tank Reactor					Stop Recovery of Product Stop Recovery of T.P. CIP SIP	9.95 9.95 Y Y Y
148 Reduced Bed Reactor	Process Inlet Temp Process Final Temp Utility Inlet Temp	37 Degree C 34 Degree C 2 Degree C	Exposure Time	50% Hours	Stop Recovery of Product Stop Recovery of T.P.	9.95 100%

A6

Unit Operation Type	Group 1			Group 2			Group 3		
	Parameter	Scn.		Parameter	Scn.		Parameter	Scn.	
	Utility Final Temp		5 Degree C				Temperature Regulation		Y
	Product Separation		9 A 0.0m				Cap		Y
	Product Separation		9 A 0.0m				SP		Y
50 Liquid/Liquid Extraction	Liquid/Liquid Ratio		1 L Extractant/ Product	Flow Composition Time		100% Hours	Stop Recovery of Product		0.8
	Product Separation		4 C	Product Phase (Top/Bottom)		Top	Stop Recovery of T.P.		50%
	Additional Duration		0.5 Hours	Harvest Time		0.5 Hours	Temperature Regulation		Y
	Additional Mix Duration		4 Hours				Cap		Y
	Mix Energy		0.3 HP/100 L				SP		Y
60 Solid/Liquid Extraction	Liquid/Liquid Ratio		1 L Extractant/ Product	Flow Composition Time		100% Hours	Stop Recovery of Product		0.8
	Product Separation		4 C	Product Phase (Top/Bottom)		Top	Stop Recovery of T.P.		50%
	Additional Duration		4 Hours	Harvest Time		0.5 Hours	Temperature Regulation		Y
	Mix Energy		0.3 HP/100 L				Cap		Y
							SP		Y



## Combined Declaration and Power of Attorney for Patent Application

Docket Number: 1606.0020001

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled **System and Method for Simulation, Modeling and Scheduling of Solution Preparation in Biopharmaceutical Batch Process Manufacturing Facilities**, the specification of which is attached hereto unless the following box is checked:

- ☐ was filed on \_\_\_\_\_;  
as United States Application Number or PCT International Application Number \_\_\_\_\_; and  
was amended on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application, which designated at least one country other than the United States listed below, and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Claimed

_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Application No.)	(Country)	(Day/Month/Year Filed)		
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Application No.)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

<u>60/050,294</u>	<u>June 20, 1997</u>
(Application No.)	(Filing Date)
_____	_____
(Application No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or under § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56 that became available between the filing date of the prior application and the national or PCT international filing date of this application.

_____	_____	_____
(Application No.)	(Filing Date)	(Status - patented, pending,
abandoned)		
_____	_____	_____
(Application No.)	(Filing Date)	(Status - patented, pending,
abandoned)		

**Appl. No. To be assigned**  
**Docket No. 1606.0020001**

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Robert G. Sterne, Esq., Reg. No. 28,912; Edward J. Kessler, Esq., Reg. No. 25,688; Jorge A. Goldstein, Esq., Reg. No. 29,021; Samuel L. Fox, Esq., Reg. No. 30,353; David K.S. Cornwell, Esq., Reg. No. 31,944; Robert W. Esmond, Esq., Reg. No. 32,893; Tracy-Gene G. Durkin, Esq., Reg. No. 32,831; Michele A. Cimbala, Esq., Reg. No. 33,851; Michael B. Ray, Esq., Reg. No. 33,997; Robert E. Sokohl, Esq., Reg. No. 36,013; Eric K. Steffe, Esq., Reg. No. 36,688; and Michael Q. Lee, Esq., Reg. No. 35,239.

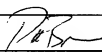
Send Correspondence to.

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.  
1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934

Direct Telephone Calls to:

(202) 371-2600

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor <b>Peter G. BROWN</b>
Inventor's signature  Date <b>6/17/98</b>
Residence <b>63 Clearwater Road, Newton, MA 02162</b>
Citizenship <b>U.S.A.</b>
Post Office Address <b>Same as above</b>

P:\USERS\VELADER\MILLER\16060020001.doc  
1027 Nov 17, 1998

(Supply similar information and signature for subsequent joint inventors, if any)